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INVESTIGATING THE MULTISENSORY REPRESENTATION OF THE HAND AND THE SPACE AROUND IT USING FMRI

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ABSTRACT

The human brain incessantly receives a staggering amount of information from all our senses. The dynamic integration of relevant multisensory signals is an evolutionarily optimal strategy to assist adaptive behavior. Arguably, one physical object stands out as the unique recipient of internal and external multisensory signals alike: the body. Recent progress within neurology, psychology, and neuroscience has emphasized the role of multisensory mechanisms in the construction of a coherent neural representation of the body and its surrounding space. In turn, this representation supports essential defensive and goal-directed behaviors, facilitates the processing of incoming sensory signals, and may lead to the emergence of the feeling of ownership of the body, a foundation of self-awareness. However, the experimental accounts of the neural mechanisms underlying the construction of this central multisensory representation of the body and its link to self-perception remain unclear.

The aim of the work presented in this thesis was to employ functional magnetic resonance imaging to pinpoint the neural multisensory representation of the hand and the space around it. Furthermore, this thesis aims at relating these multisensory mechanisms to the self-perception of the hand through the interpretation of converging behavioral, neural, and physiological measures. In **Studies I**, **II**, and **V**, we used a combination of ecologically valid paradigms and setups based on virtual reality technology to characterize a set of interconnected premotor, posterior parietal, and subcortical regions that integrate congruent visual, somatosensory, and proprioceptive signals from the upper limb. Furthermore, we provided evidence for the idea that the representation of the hand forms multisensory predictions about self-specific incoming sensory events. In **Studies III** and **IV**, we implemented an fMRI-adaptation paradigm to gain evidence of the existence of neuronal populations in the hand-related multisensory areas with visual receptive fields restricted to the space close to the hand and anchored to the upper limb.

Complementary neural, behavioral, and physiological measures consistently related these multisensory mechanisms to the feeling of ownership of the hand, which is contingent upon the spatio-temporal congruence of multisensory signals within the perihand space. In conclusion, the experiments presented in this thesis describe a set of multisensory brain regions that draw from multiple sensory modalities to build a self-specifying representation of the hand and the space around it. These results are interpreted with respect to earlier findings in non-human primates and humans, and the key functions of this representation, including its role in supporting essential behaviors and the multifaceted self-perception of the hand.

LIST OF PUBLICATIONS

I. **Gentile G**, Petkova VI, Ehrsson HH. Integration of visual and tactile signals from the hand in the human brain: an fMRI study. *Journal of Neurophysiology* (2011), 105:910-22.

II. **Gentile G**, Guterstam A, Brozzoli C, Ehrsson HH. Disintegration of multisensory signals from the real hand reduces default limb self-attribution: an fMRI study. *Journal of Neuroscience* (2013), 33:13350-66.

III. Brozzoli C* & **Gentile G***, Petkova VI, Ehrsson HH. fMRI adaptation reveals a cortical mechanism for the coding of space near the hand. *Journal of Neuroscience* (2011), 31:9023-31. ***Equal contribution**.

IV. Brozzoli C* & **Gentile G***, Ehrsson HH. That's near my hand! Parietal and premotor coding of hand-centered space contributes to localization and self-attribution of the hand. *Journal of Neuroscience* (2012), 32:14573-82. ***Equal contribution**.

V. **Gentile G**, Guterstam A, Ehrsson HH. Self-specific multisensory prediction error signals in the human brain. *Manuscript*.

LIST OF ADDITIONAL PUBLICATIONS

I. Petkova VI, Björnsdotter M*, **Gentile G***, Jonsson T, Li TQ, Ehrsson HH. From part to whole-body ownership in the multisensory brain. *Current Biology* (2011), 21:1-5. ***Equal contribution**.

II. Brozzoli C, **Gentile G**, Bergouignan L, Ehrsson HH. A shared representation for the space near oneself and another person in the human ventral premotor cortex. *Current Biology* (2013), 23:1764-68.

III. Guterstam A, **Gentile G**, Ehrsson HH. The invisible hand illusion: multisensory integration leads to the embodiment of a discrete volume of empty space. *Journal of Cognitive Neuroscience* (2013), 25:1078-99.

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LIST OF ABBREVIATIONS

AIP	Anterior IntraParietal
BOLD	Blood Oxygen Level Dependent
CS	Central Sulcus
EBA	Extrastriate Body Area
fMRI	Functional Magnetic Resonance Imaging
HMD	Head Mounted Displays
IFS	Inferior Frontal Sulcus
INS	Insula
IPS	IntraParietal Sulcus
LIP	Lateral IntraParietal
LOC	Lateral Occipital Cortex
LOS	Lateral Occipital Sulcus
MIP	Medial IntraParietal
MRI	Magnetic Resonance Imaging
PMd	Dorsal Premotor Cortex
PMv	Ventral Premotor Cortex
PoCG	Post Central Gyrus
PoCS	Post Central Sulcus
PrCS	Pre Central Sulcus
RF	Receptive Field
SCR	Skin Conductance Response
SMG	SupraMarginal Gyrus
SVC	Small Volume Correction
VIP	Ventral IntraParietal

1 LAYPERSON'S SUMMARY

Few things are as entrenched in our perceptual experience of the world as our physical body. The hand is the most common vehicle for our interactions with others and with the environment, and yet we don't often find ourselves consciously pondering the question of just how it is that we experience the hand as belonging to our body. Likewise, we don't consciously perceive any boundary between the space close to our hands, where we routinely interact with objects, and the space outside of our reach. Nonetheless, these questions represent computational problems that the human brain has to solve in order to support some evolutionarily crucial aspects of our physical existence, such as protecting the body from potential threats and interacting with other individuals and with the environment.

The work presented in this thesis is a modest attempt to provide experimental evidence in support of theoretical models that explain how the human brain might solve these problems. The focus of the work presented here is on the idea that the brain continuously combines information from our senses (like vision, touch, and the sense of position) to construct and dynamically update a model of the hand and the immediate space around it. In turn, this model helps us predict and interpret incoming sensory information, guides actions performed with the hand, and possibly even leads to the emergence of the feeling of "ownership" of the hand. To test these ideas, we used functional magnetic resonance imaging, together with behavioral and physiological techniques, to non-invasively measure brain activity in healthy humans evoked by sensory stimuli delivered to their right hand and the immediate space around it.

In a series of experiments, we consistently found that the integration of information from multiple sensory modalities (i.e., "multisensory" information) underpins the construction of a model of the hand and the space around it. Furthermore, our results suggest that the feeling of ownership of the hand relies on multisensory signals that correspond in time and space, and on the predictions that the brain makes about incoming sensory information. These results are important as they contribute to our understanding of some fundamental aspects of the experience of our physical self and of the clinical conditions in which this experience is significantly disrupted.

2 INTRODUCTION

At any given time, the human brain receives a staggering amount of information from our senses. The ability to filter and process the sensory signals that are relevant for behavior is an essential requirement for any living organism. The combination of the inputs to multiple sensory channels is an evolutionarily optimal strategy to facilitate adaptive behavior, as implied by the ubiquity of multisensory processes across species, including insects (Hengstenberg, 1993; Gilbert and Kuenen, 2008; Frye, 2010), fish (González et al., 1999; Gardiner and Atema, 2007; Sankrithi, 2010; Gardiner and Motta, 2012), birds (Korzeniewska, 1987; Reches and Gutfreund, 2009; Zahar et al., 2009), rodents (Fortis-Santiago et al., 2010; Cohen et al., 2011; Gleiss and Kayser, 2012; Ravassard et al., 2013), cats (Meredith and Stein, 1986; Stein and Stanford, 2008; Perrault et al., 2012), non-human primates (Rizzolatti et al., 1981a, 1981b; Duhamel et al., 1998; Graziano et al., 2000; Avillac et al., 2005), and humans (Calvert et al., 2004; Ernst and Bülthoff, 2004; Driver and Noesselt, 2008; Murray and Wallace, 2012).

Multisensory processes are such a pervasive feature of neuronal processing that scientists contemplate whether the entire cortical apparatus is essentially multisensory (Ghazanfar and Schroeder, 2006; Driver and Noesselt, 2008). In the midst of our multisensory perceptual experience of the world, one physical object stands out as the unique locus of convergence of sensory signals: the body (James, 1890; Merleau-Ponty, 1962; Gibson, 1986; Graziano and Botvinick, 2002; Gallagher, 2006; Heed and Röder, 2012). Evolution has empowered the brain's sensory structures with what is arguably the most critical aspect of adaptive behavior: the ability to efficiently identify one's own body in the environment. The distinction between the body and the environment is a *sine qua non* prerequisite for evolutionarily relevant behaviors like the protection of the body from potential threats (Graziano and Botvinick, 2002) and the ability to interact with objects and other individuals (van den Bos and Jeannerod, 2002; Ernst and Bülthoff, 2004; Stein and Stanford, 2008), but likely extends, based on converging developments in both philosophy and experimental science, to the very foundation of our experience as a unified entity in the world (Merleau-Ponty, 1962; Gibson, 1986; Bermudez, 1998; Jeannerod, 2004; Gallagher, 2006; Ehrsson, 2007; Blanke and Metzinger, 2009; Frith, 2013).

Recent developments in psychology and cognitive neuroscience have identified the body's unique status as the locus of convergence of multisensory signals as the origin of the mechanisms that support the construction of the corporeal experience of oneself in the world (Merleau-Ponty, 1962; Jeannerod, 2004; Gallagher, 2006; Blanke, 2012; Ehrsson, 2012). For instance, these theories posit that specific patterns of multisensory correlations enable the brain to distinguish the body from the environment (Graziano and Botvinick, 2002; Makin et al., 2008) and to discriminate self-initiated actions from the motor behavior of others (Blakemore et al., 1998; van den Bos and Jeannerod, 2002; Jeannerod, 2004; Frith, 2012). Thanks to recent breakthroughs in clinical neuropsychology, experimental psychology, and cognitive neuroscience, a consensus has emerged for the key role of multisensory mechanisms in leading to the emergence of the "feeling of ownership" or "self-attribution" of one's physical body (Botvinick and Cohen, 1998; Ehrsson et al., 2004; Petkova and Ehrsson, 2008; Tsakiris, 2010; Blanke, 2012; Ehrsson, 2012), defined as the perceptual experience of the body as belonging to oneself, which represents a key feature of self-consciousness.

The above considerations advocate the existence of multisensory mechanisms that enable the brain to construct, maintain, and update a central representation of the body. This representation draws from multiple sensory modalities, like vision, touch, and the sense of position, to support essential behavior, including but not limited to defensive and goal-directed interactions with environment. Furthermore, there are strong reasons to believe that this multisensory representation of the body may serve as the platform for the emergence of higher-level features of the perceptual experience of the body, like the conscious feeling of ownership or self-attribution of the body. Despite the evidence that has been gathered to portray the scenario illustrated above, the investigation of the neural mechanisms underlying the multisensory representation of the body in the brain and its link to the self-perception of the body is a surprisingly recent scientific endeavor within cognitive neuroscience (Blanke, 2012; Ehrsson, 2012; Heed and Röder, 2012).

The work presented in this thesis is a modest attempt to provide evidence in support of theoretical models that attempt to explain how the brain combines information from the different sensory modalities to build and maintain a coherent representation of the body that supports essential behavioral functions. Furthermore, the work presented here aimed at providing experimental support for the notion that the successful integration of information from multiple sensory modalities leads to the emergence of the unified self-perception of one's own body. The object of investigation throughout this thesis is the human hand, which serves as an excellent experimental model for converting the above ideas into testable hypotheses. The functional significance of the plethora of behaviors that are mediated by the hands (Ehrsson et al., 2000; Rizzolatti and Luppino, 2001; Graziano and Botvinick, 2002; Fogassi and Luppino, 2005; Culham and Valyear, 2006; Johansson and Flanagan, 2009) is mirrored by the disproportionally large resources that the central nervous system devotes to the representation of the hands, as opposed to other parts of the body (Penfield and Jasper, 1954; Anon, 1996; Mountcastle, 2005; Wilson, 2010). Accordingly, the available evidence that motivated the work presented in this thesis is most abundant for the upper limbs than for other body parts, permitting the formulation of more specific hypotheses. In the following sections, I will synthesize the evidence in favor of the existence of a central multisensory representation of the hand that draws from the sensory signals from the upper limb and its surrounding space, and how these mechanisms might be related to the self-perception of the hand. The following section will begin with a summary of the neurophysiological literature that has characterized the multisensory mechanisms for the integration of sensory signals from the body and the space around it. Next, I will bring together evidence from clinical neuropsychology, behavioral, and neuroimaging research in healthy and diseased humans to provide an overview of the current knowledge about equivalent multisensory mechanisms in the human brain. In the process, I will outline the outstanding open questions that have been translated into the specific hypotheses behind the work presented in the thesis.

2.1 MULTISENSORY INTEGRATION: IT ALL STARTED WITH THE CAT'S SUPERIOR COLLICULUS

The neuroscientific investigation of the neurophysiological mechanisms underlying multisensory integration began with a series of seminal studies of the cat's superior colliculus, a subcortical structure known to play an important role in the sensorimotor guidance of behavior (Meredith and Stein, 1986, 1996; Stein and Stanford, 2008; Perrault et al., 2012). These studies characterized individual neurons with receptive fields in multiple sensory modalities, such as vision, audition, and somatosensation. The convergence of information from different sensory channels onto the same nerve cells provides a neural substrate for the dynamic integration of the senses, an essential requirement for the coordination of ecologically relevant behavior (Ernst and Bülthoff, 2004; Stein and Stanford, 2008). The neuronal computations performed by these neurons in the superior colliculus have been examined primarily by comparing the electrophysiological responses to unisensory signals with the firing rates evoked by multisensory stimuli. This has revealed the ability of individual multisensory neurons to combine unisensory signals in a variety of operational modes, including linear and non-linear combinations of the inputs (Meredith and Stein, 1996; Stanford and Stein, 2007; Stein and Stanford, 2008). Specifically, additive or subadditive multisensory response profiles are characterized by firing rates evoked by multisensory stimuli that do not exceed the algebraic sum of the firing rates evoked by the unisensory stimuli presented in isolation. Conversely, non-linear (*superadditive*) firing rates to multisensory stimuli significantly exceed the sum of the firing rates evoked by the unisensory stimuli.

The dynamic electrophysiological properties of these neurons, together with the spatial alignment of their multisensory receptive fields, enable the efficient filtering of afferent sensory information, facilitating the selection of the behaviorally relevant signals that are to be integrated. A number of key principles have emerged that regulate the neuronal integration of multisensory signals (Stein and Stanford, 2008). The *temporal* principle refers to the increased likelihood for multisensory signals to be combined if they occur within a restricted temporal window, whereas the *spatial* principle points to the enhanced integration of signals originating from a common region of space. Furthermore, the principle of *inverse effectiveness* posits that the less effective the individual unisensory signals, the greater the behaviorally significant advantage obtained from their integration. These principles, first outlined through the electrophysiological classification of single neurons in the anesthetized cat's superior colliculus, have been extended to the exploration of multisensory mechanisms in many neuroscientific disciplines, playing a pivotal role in experiments ranging from neurophysiological studies in non-human primates to behavioral, neuropsychological, and neuroimaging research in humans (Ernst and Bülthoff, 2004; Holmes and Spence, 2005a; Driver and Noesselt, 2008; Murray and Wallace, 2012).

2.2 INSIGHTS FROM NEUROPHYSIOLOGICAL RESEARCH IN NON-HUMAN PRIMATES

Of particular relevance to the hypotheses that motivated the research presented in this thesis are the insights obtained from neurophysiological studies of multisensory integration in non-human primates. In particular, the experimental accounts of how sensory inputs from the body and its surrounding space are combined in multisensory frontal, parietal, and subcortical brain areas played a major role in shaping the theoretical framework against which the present experiments were designed and interpreted. Over the past few decades, individual neurons have been described in the non-human primate's brain with tactile receptive fields centered on a body part, such as the hand or the head, and with visual receptive fields that encompass the space abutting it. These multisensory visuo-tactile receptive fields allow individual neurons to be responsive to tactile stimuli applied to the corresponding portion of the monkey's body, to afferent proprioceptive signals from the same body part, and to visual stimuli that originate in the space surrounding it. These neurons respond preferentially to visual and tactile signals that are spatio-temporally congruent, i.e., that occur within a restricted temporal window and originate from a common region of the body and the space around it (Duhamel et al., 1998; Avillac et al., 2005, 2007), and are sensitive to matching visual and proprioceptive signals concerning the position of that body part in space (Graziano, 1999; Graziano et al., 2000). Furthermore, the electrophysiological responses of these neurons to congruent multisensory signals exhibit linear and non-linear response profiles that are reminiscent of the multisensory responses found in the cat's superior colliculus (Meredith and Stein, 1996; Stanford and Stein, 2007). Visuo-tactile neurons with these properties have been described in a number of cortical and subcortical areas, including the ventral intraparietal area (VIP) in the depth of the intraparietal sulcus (Colby and Duhamel, 1991; Colby et al., 1993a, 1993b; Duhamel et al., 1998; Avillac et al., 2005, 2007), in areas 5 (Sakata et al., 1973; Iriki et al., 1996; Graziano et al., 2000) and 7b of the inferior parietal lobe (Hyvärinen and Poranen, 1974; Hyvärinen, 1981), in the upper bank of the superior temporal sulcus (Bruce et al., 1981, 1986; Desimone et al., 1984), in the premotor cortex (Rizzolatti et al., 1981a, 1981b; Graziano et al., 1997; Fogassi et al., 1999; Graziano and Gandhi, 2000), and in the putamen (Graziano and Gross, 1993).

The visual RFs of these multisensory neurons are usually restricted to the space extending from the body surface to approximately 5-30 cm from the location of the tactile receptive fields, forming a single responsive unit that encodes the presence of sensory stimuli on a body part and the space surrounding it, known as the peripersonal space (Rizzolatti et al., 1981a, 1981b; Fogassi et al., 1999). These neurons also receive afferent proprioceptive inputs from the corresponding body part, enabling the spatial remapping of the visual RFs when the body part changes position in space (Andersen et al., 1997; Graziano et al., 1997, 2000; Graziano, 1999; Graziano and Botvinick, 2002). Thus, the multisensory representation of the peripersonal space is body-part-centered, i.e., spatially anchored to the body part, constructing a spatial reference frame distinct from those centered on other body parts or on retinotopical and allocentric coordinates (Rizzolatti et al., 1981a, 1981b; Andersen et al., 1997; Duhamel et al., 1998; Graziano, 1999; Graziano et al., 2000; Graziano and Botvinick, 2002; Avillac et al., 2005).

The neuronal populations reviewed above form densely interconnected circuits that span frontal, parietal, and subcortical areas. Direct and indirect anatomical connections have been described between the anterior and medial segments of the intraparietal sulcus (Grefkes and Fink, 2005; Culham et al., 2006), parietal areas 2 and 5 (Pandya and Kuypers, 1969; Neal et al., 1988; Andersen et al., 1997), the posterior superior parietal gyrus (Mountcastle et al., 1975; Iriki et al., 1996; Graziano et al., 2000), the inferior parietal cortex (Hyvärinen and Poranen, 1974; Luppino et al., 1999; Luppino and Rizzolatti, 2000), the parietal operculum and the insula (Hyvärinen, 1982; Neal et al., 1990a, 1990b), the premotor cortex (Rizzolatti et al., 1981a, 1981b; Fogassi et al., 1999; Graziano and Gandhi, 2000), the putamen (Künzle, 1978; Weber and Yin, 1984; Cavada and Goldman-Rakic, 1991; Parthasarathy et al., 1992; Graziano and Gross, 1993), and the cerebellum (Murphy et al., 1973; Glickstein et al., 1994; Dum and Strick, 2003; Ramnani, 2006; Sultan and Glickstein, 2007). All of the above regions also receive direct and indirect inputs from early sensory cortices, including tactile, visual, and proprioceptive signals (Graziano and Botvinick, 2002), and send direct and indirect projections to the motor cortices (Rizzolatti and Luppino, 2001). Thus, the multisensory neuronal populations in the above regions are ideally suited to integrate sensory inputs from the body and its surrounding space, maintain their receptive fields aligned, and serve as a sensorimotor interface for the planning and performance of interactions with objects and other individuals in the environment.

What are the main functions of the multisensory circuits described above? Their functional and anatomical properties provide the brain with a mechanism to combine sensory information from the body and the external world with vital motor functions. From an evolutionary perspective, the multisensory representation of the body and its surrounding space appears ideally suited to serve as the neural platform for the coordination of two essential functions: the protection of the body from external threats and the interaction with objects in the environment (Andersen et al., 1997; Graziano and Botvinick, 2002; Fogassi and Luppino, 2005; Culham and Valyear, 2006). Dodging potential threats directed towards the head or the arms, for example, requires that visual information be combined with tactile and proprioceptive signals to map an external event in body-centered reference frames. In turn, this triggers the appropriate sensorimotor transformations that select, plan, and execute the required motor plan. Indeed, the electrical stimulation of multisensory neurons in the non-human primate's brain leads to the initiation of complex movements compatible with defensive acts (Graziano et al., 2002; Cooke and Graziano, 2003; Cooke et al., 2003). Furthermore, the dynamic ability to encode the location of an object in body-centered coordinates is an essential passage in the cascade of the sensorimotor transformations that allow the brain to plan and implement a variety of goal-directed actions towards relevant targets, such as reaching, grasping, and manipulating objects in the space surrounding the body (Andersen et al., 1997; Johansson et al., 2001; Rizzolatti and Luppino, 2001; Graziano and Botvinick, 2002; Flanagan and Johansson, 2003; Culham et al., 2006; Brozzoli et al., 2012). Intriguingly, the multisensory properties of these neuronal populations may also facilitate the use of tools to extend the repertoire of possible actions and project motor affordances to what would otherwise be extrapersonal space (Iriki et al., 1996; Maravita and Iriki, 2004; Culham and Valyear, 2006; Cardinali et al., 2009b; Valyear et al., 2012; Gallivan et al., 2013). The above considerations support the notion that the multisensory representation of the body and its surrounding space has developed to facilitate evolutionarily essential behavioral functions. What is known about the existence of equivalent mechanisms in the human brain?

2.3 NEUROPSYCHOLOGICAL EVIDENCE IN CLINICAL POPULATIONS

Valuable insights on the neural mechanisms underpinning the integration of sensory signals from the body and the peripersonal space and its relationship with the self-perception of the hand come from the neuropsychological literature. By investigating the changes in behavior and physiology that are associated with neurological damage to specific regions of the human brain, neuropsychologists have gathered evidence that has inspired a wealth of behavioral and neuroimaging research in healthy participants. The neuropsychological studies that provided the strongest evidence for the existence of a selective multisensory representation of the space near the body have capitalized on two syndromes known as spatial neglect and extinction (Bender, 1977; di Pellegrino et al., 1997; Làdavas and Farnè, 2004; Brozzoli et al., 2006; Vallar, 2007; Jacobs et al., 2012; Karnath and Rorden, 2012).

Spatial neglect is a neuropsychological condition typically associated with damage in the right posterior parietal lobe and manifesting as reduced awareness and ability to process sensory stimuli presented in the hemisphere contralateral to the lesion site (Karnath and Rorden, 2012; Newport and Schenk, 2012). Neglect is typically not associated with specific deficits in basic sensory processing and affects selectively either the space near the body or the extrapersonal space (Halligan and Marshall, 1991; Berti and Frassinetti, 2000; Làdavas and Farnè, 2004; Macaluso and Maravita, 2010). This advocates the existence of segmented spatial representations that distinguish between the peripersonal and the extrapersonal space, a distinction that is typically not the object of conscious awareness. The interaction between visual and proprioceptive signals that underlies the use of prism adaptation to alleviate some of the symptoms of neglect (Rossetti et al., 1998; Redding and Wallace, 2006; Serino et al., 2007; Newport and Schenk, 2012) is further evidence in support of the multisensory nature of the representation of the body and the space around it that is damaged in patients suffering from this syndrome (Làdavas and Farnè, 2004; Jacobs et al., 2012).

Additional evidence for the selective multisensory representation of the hand and its surrounding space comes from studies in patients suffering from extinction. In this neurological syndrome, lesions affecting the right cerebral hemisphere lead to a loss of awareness with respect to sensory stimuli presented in the contralesional side of space, only when these are paired with the simultaneous presentation of another sensory event in the ipsilateral hemispace (Bender, 1977; Brozzoli et al., 2006; Nachev and Husain, 2006; Macaluso and Maravita, 2010; de Haan et al., 2012). In other words, the conscious perception of a contralateral sensory stimulus is “extinguished” by the co-occurrence of an ipsilateral sensory event. Crucially, extinction has been to shown to extend to the interaction of signals from different sensory modalities, like vision and touch, to be restricted to the space near the hand, and to operate in a reference frame that is spatially anchored to the upper limb (di Pellegrino et al., 1997; Làdavas and Farnè, 2004; Farnè et al., 2005; Sarri et al., 2006; Kennett et al., 2010). These neurological observations provide support for the notion that the human brain builds a selective representation of the peripersonal space across multiple sensory modalities, in agreement with the correspondent mechanisms in the brain of non-human primates reviewed above. What type of neuropsychological evidence links these multisensory mechanisms to the self-perception of the body?

The neurological condition known as somatoparaphrenia is an important source of evidence supporting the notion that the self-perception of the body is a central construct that relies on unimpaired neural circuits (Gerstmann, 1942; Berti et al., 2005; Arzy et al., 2006; Vallar and Ronchi, 2009; Feinberg et al., 2010; Blanke, 2012; Ehrsson, 2012; Moseley et al., 2012). Patients diagnosed with somatoparaphrenia suffer from monothematic delusions of bodily self-perception and report the lack of ownership over a contralesional paralyzed body part, denying that it belongs to their own body even if confronted with ample evidence that suggests otherwise (Vallar and Ronchi, 2009). Somatoparaphrenia is a striking neurological syndrome that goes beyond deficits in basic sensory processing (such as hemianesthesia, an impairment in the processing of somatosensory stimuli from a contralesional body part) and associated syndromes like asomatognosia that are characterized by the temporarily reversible failure to identify the contralesional limb as belonging to one's body (Vallar and Ronchi, 2009; Feinberg et al., 2010). Neuroanatomically, somatoparaphrenia and related syndromes have been associated with widespread lesions spanning the frontal, parietal, and temporal cortices, predominantly in the right hemisphere (Berti et al., 2005; Vallar and Ronchi, 2009; Feinberg et al., 2010; Blanke, 2012), though the experimental findings tend to diverge, with emphasis been placed on several brain structures, including the right temporo-parietal cortex (Halligan et al., 1995; Vallar and Ronchi, 2009; Feinberg et al., 2010), the right posterior insula (Karnath et al., 2005; Baier and Karnath, 2008; Karnath and Baier, 2010; Heydrich and Blanke, 2013), the orbitofrontal cortex (Feinberg et al., 2010), the premotor cortex (Arzy et al., 2006; Zeller et al., 2011), and subcortical and white matter structures (Gandola et al., 2012; Invernizzi et al., 2013).

The description of neuropsychological conditions like spatial neglect, extinction, and somatoparaphrenia supports (1) the existence of a multisensory representation of the body and its surrounding space, and (2) the notion that the feeling of ownership of one's body is a central construct maintained by the unimpaired state of the higher-order association cortices. However, the neuropsychological observations recapped above are fragmented, usually involve large lesions that span multiple cortical, subcortical, and white matter structures, and are not informative about the specific neural mechanisms that are impaired in these syndromes. In light of this, it becomes essential to scrutinize the behavioral and neuroimaging literatures in healthy humans to be able to formulate more specific hypotheses concerning the multisensory mechanisms, as well as the corresponding brain structures and functions, that support the unimpaired self-perception of one’s own body.

2.4 BEHAVIORAL EVIDENCE IN HEALTHY HUMANS

Multisensory mechanisms are a pervasive feature of brain function and play a key role in facilitating adaptive behavior and shaping our perception of ourselves and the environment (Ernst and Bülthoff, 2004; Driver and Noesselt, 2008; Stein and Stanford, 2008). The associated behavioral literature is vast and spans many domains of cognitive science (Calvert et al., 2004; Murray and Wallace, 2012). In the following paragraphs, I will summarize the behavioral evidence that is most pertinent to the investigation of the mechanisms associated with the integration of visual, tactile, and proprioceptive signals from the hand, and how these mechanisms may support the self-perception of the hand.

A behavioral paradigm that has provided valuable insights on the interaction of visual and tactile signals from the hand, as well as on the existence of a hand-centered representation of the perihand space, is the crossmodal congruency effect (Spence et al., 2004b; Shore et al., 2006; Spence, 2011). In the original version of this paradigm, the participant receives somatosensory (typically vibrotactile) stimuli at one of two different target locations on the hand, and a simultaneous task-irrelevant visual stimulus presented in the vicinity of one of the target locations. The behavioral effect, expressed as the reaction time to a detection task associated with the spatial location of the tactile stimulus, differs significantly between trials in which the task-irrelevant visual stimulus is presented at a location congruent, as opposed to incongruent, to the location of the tactile stimulus. The crossmodal congruence effect, calculated as the difference in the average reaction time between the incongruent and the congruent trials, serves as a proxy of the degree of interaction between visual and tactile signals from the hand (Holmes et al., 2004; Spence et al., 2004b; Macaluso and Maravita, 2010; Brozzoli et al., 2012). The observations that the crossmodal congruence effect decreases as a function of the distance between the visual and the tactile stimuli (Spence et al., 2004a), and that it operates in a hand-centered coordinate system (Spence et al., 2004b), constitute indirect behavioral evidence for the existence of a representation of the space close to the hand, restricted in spatial extent and centered on the upper limb (Macaluso and Maravita, 2010; Brozzoli et al., 2012). Furthermore, behavioral research employing prism adaptation or mirrors has stressed the role of visual and proprioceptive signals in localizing the hand in space, providing additional behavioral evidence in support of the existence of a central multisensory representation of the hand that draws from multiple sensory modalities (Lackner and DiZio, 2000; Spence et al., 2004b; Holmes and Spence, 2005b; Holmes et al., 2006; Snijders et al., 2007) to support behaviorally relevant sensorimotor mechanisms.

Recent behavioral evidence has reinforced the notion that visual and tactile stimuli in the space near the hand are represented in a reference frame that is centered on the upper limb and that serves as a functional interface to guide interactions with objects within reach of the hand (Brozzoli et al., 2012; Makin et al., 2012). Using transcranial magnetic stimulation, Makin and colleagues described how the appearance of a visual stimulus within the space close to the hand modulates the corticospinal excitability in a way that is compatible with the automatic generation of a defensive motor program encoded in hand-centered coordinates (Makin et al., 2009). This observation provides evidence for how the selective representation of objects within the perihand space may facilitate protecting the body from incoming threats, in accordance to the analogous mechanisms described in non-human primates (Cooke and Graziano, 2003; Cooke et al., 2003). Furthermore, Brozzoli and colleagues provided evidence for hand-centered visuo-tactile interactions anchored to the planning and execution of grasping actions performed with the hand (Brozzoli et al., 2009, 2010), corroborating the putative role of the representation of the perihand space as a relevant sensorimotor interface (Graziano and Botvinick, 2002; 2012; Makin et al., 2012). The evidence illustrated above informs us on the existence of multisensory integrative processes that combine sensory signals from the hand and its surrounding space to facilitate behavior. How are these lines of behavioral evidence connected to the study of the multisensory mechanisms supporting the self-attribution of the hand in healthy humans?

A breakthrough in the behavioral investigation of the multisensory nature of bodily self-perception came with the description of a striking perceptual illusion known as the rubber hand illusion (Botvinick and Cohen, 1998). In this paradigm, the delivery of temporally synchronous tactile stimuli to the participant’s hand, hidden from view, and visual stimuli on a rubber hand placed in an anatomically compatible posture in direct view of the participant elicits the referral of somatic sensations to the corresponding skin surface of the rubber hand. This is accompanied, in the majority of participants, by a subjectively reported feeling of ownership of the rubber hand (Botvinick and Cohen, 1998). The embodiment of the artificial limb is also associated with a remapping of the perceived location of the hand toward the position of the artificial limb, termed proprioceptive drift, which ranges between 10 and 20% of the distance between the veridical and artificial hands (Botvinick and Cohen, 1998). Furthermore, threats directed toward the rubber hand evoke psychophysiological responses that mirror the illusory embodiment of the limb (Armel and Ramachandran, 2003; Ehrsson et al., 2007; Guterstam et al., 2011). The seminal report of the rubber hand illusion offered an unprecedented tool to overcome one of the major limitations in the study of the psychological and neural mechanisms of bodily self-perception in healthy volunteers, that is the challenge of inducing changes in the self-perception of the body in an controlled experimental setting.

Since the original report by Botvinick and Cohen, a very large number of behavioral studies have been published on the rubber hand illusion paradigm and variations thereof. Researchers have characterized in-depth the perceptual rules that govern the illusory embodiment of the limb, including the anatomical hand-centered congruence between the visual and tactile stimuli (Costantini and Haggard, 2007), the temporal window of integration within which the illusion can be elicited (Shimada et al., 2005, 2009), the spatial boundaries of the illusion (Lloyd, 2007), the humanoid shape of the embodied object (Tsakiris et al., 2010a), and so forth. The rubber hand illusion paradigm has also been adapted to the investigation of the relationship between embodiment and the sense of agency (Tsakiris et al., 2010b; Kalckert and Ehrsson, 2012), the boundaries of the plastic representation of the body in healthy volunteers (Slater et al., 2008; Hohwy and Paton, 2010; Newport and Preston, 2010; Guterstam et al., 2011, 2013), upper limb amputees (Ehrsson et al., 2008; Schmalzl and Ehrsson, 2011; Schmalzl et al., 2011), and patients (Fiorio et al., 2011; Morgan et al., 2011; Ramakonar et al., 2011; Thakkar et al., 2011; Ferri et al., 2013b), the role of interoceptive signals (Tsakiris et al., 2011) and expectations (Ferri et al., 2013a), and even the social implications of the illusory embodiment of a body part of a different color and race (Farmer et al., 2012; Maister et al., 2013).

Researchers have also collected evidence and speculated on the neurophysiological consequences that the illusory embodiment of an artificial limb may have on the representation of the real hand. Moseley and colleagues revealed that the experience of the rubber hand illusion is associated with a drop in the skin temperature of the real hand (Moseley et al., 2008), as well as to increased levels of histamine reactivity in the real arm (Barnsley et al., 2011). These physiological observations have been interpreted as signs that the brain may "disembody" the real hand when illusorily embodying an artificial limb, but this outstanding question remains at the center of experimental debate (Folegatti et al., 2009; de Vignemont, 2011; Guterstam et al., 2011; Guterstam and Ehrsson, 2012; Moseley et al., 2012; Salomon et al., 2013). In the light of the neurophysiological evidence discussed previously, a perhaps more relevant question refers to the possibility to experimentally induce a feeling of "disownership" of the real arm, a phenomenon that would bear closer resemblance to the disturbances in the self-attribution of the hand experienced by certain clinical populations (Sacks, 1998; Berti et al., 2005; Vallar and Ronchi, 2009; Feinberg et al., 2010; de Vignemont, 2011; Gandola et al., 2012). Intriguingly, a recent behavioral experiment employed virtual reality techniques to introduce violations of the multisensory expectations related to the self-perception of the hand, and reported that the failure to integrate visual, tactile, and proprioceptive signals from the real upper limb led to the transient loss of ownership of the hand (Newport and Gilpin, 2011). This observation hints at the intriguing possibility to be able to induce changes in the self-attribution of the veridical hand by experimentally manipulating the congruence of the sensory signals from the upper limb. These findings suggest a potential new avenue for the research on the multisensory mechanisms of bodily self-attribution, where changes in the latter are studied in relation to the real body, the "one that is always there" (James, 1890), as opposed to resorting to the limiting, albeit very informative, use of perceptual illusion (Botvinick, 2004; Moseley, 2011; Newport and Gilpin, 2011).

The multisensory integrative principles that support the embodiment of a limb have been extended to the embodiment of the entire body (Petkova and Ehrsson, 2008; Slater et al., 2009; Petkova et al., 2011b; van der Hoort et al., 2011). Petkova and colleagues revealed that congruent visuo-tactile signals delivered to the participant's body and to the body of a humanoid mannequin observed from the first person perspective induce a feeling of ownership of the artificial body (Petkova and Ehrsson, 2008; Petkova et al., 2011b). Similar multisensory effects seem to support the spatial localization of the physical self, as demonstrated by the striking perceptual induction of so-called "out-of-body" experiences in healthy volunteers (Ehrsson, 2007; Lenggenhager et al., 2007;

Guterstam and Ehrsson, 2012). In these paradigms, healthy volunteers are exposed to temporally synchronous tactile stimuli on their veridical body and visual stimuli presented via head-mounted displays from a first person perspective other than that of the veridical body. As a consequence, most participants report a vivid sense of being located “outside” their veridical body (Ehrsson, 2007; Guterstam and Ehrsson, 2012), possibly experiencing disownership of the latter (Guterstam and Ehrsson, 2012). These behavioral paradigms stress the role of multisensory mechanisms in supporting another key aspect of bodily awareness, that is the perceived spatial location of one’s own physical self (Serino et al., 2013). The behavioral literature reviewed above, inspired by neuropsychological observations in clinical populations, provides considerable evidence in favor of the pivotal role played by multisensory mechanism in the representation of the body and the peripersonal space, as well as in the emergence of the multifaceted corporeal experience of the self. What is known about the putative neural mechanisms that support these fundamental aspects of bodily self-perception?

2.5 NEUROIMAGING EVIDENCE IN HUMANS

Over the past decade, the use of neuroimaging methods like fMRI has been gaining substantial momentum in attempting to characterize multisensory integrative processes in the human brain (Ernst and Bülthoff, 2004; Driver and Noesselt, 2008; Murray and Wallace, 2012). Research efforts have been particularly fruitful in the investigation of themes like auditory-visual integration and speech processing (Calvert et al., 2000, 2001; Noesselt et al., 2007; Stevenson et al., 2007; van Atteveldt et al., 2010; Werner and Noppeney, 2010, 2011; Marchant et al., 2012; Nath and Beauchamp, 2012), visuo-haptic integration for the representation of objects (Amedi et al., 2001; Amedi, 2002; Sathian, 2005; Lacey et al., 2007, 2009; Tal and Amedi, 2009; Naumer et al., 2010), visuo-proprioceptive integration for the planning and performance of goal-directed actions (Culham et al., 2006; Rice et al., 2007; Bernier and Grafton, 2010; Cavina-Pratesi et al., 2010; James et al., 2011; Monaco et al., 2011), and crossmodal attentional mechanisms (Macaluso et al., 2000, 2005; Macaluso and Driver, 2005; Talsma et al., 2010). Besides describing the convergence of signals from different sensory modalities in higher-order association areas, human neuroimaging studies have described how the interplay between the senses seems to be a pervasive feature of neuronal computations spanning higher-order areas as well as primary sensory cortices. Where does the knowledge derived from the human neuroimaging literature stand when it comes to the mechanisms underpinning the integration of signals from the body and the peripersonal space and its role in the self-perception of the body?

Several neuroimaging studies have presented evidence for the convergence of visual and tactile signals onto frontal, parietal, and subcortical brain regions (Hadjikhani and Roland, 1998; Banati, 2000; Lloyd et al., 2003; Saito et al., 2003; Blake et al., 2004; Sereno and Huang, 2006; Sarri et al., 2006; Makin et al., 2007; Nakashita et al., 2008; Beauchamp et al., 2010; Huang et al., 2012). The detailed comparison of human neuroimaging data with the neurophysiological findings in non-human primates is inherently limited by the difficulties in establishing homological relations (Grefkes and Fink, 2005; Culham and Valyear, 2006). A few studies have suggested that visual and tactile signals from the face converge in regions of the parietal cortex that seem to be analogous to those described in non-human primates. Bremmer and colleagues (Bremmer et al., 2001) demonstrated significant overlap of the BOLD responses evoked by the delivery of air puffs to the face, two-dimensional digital visual stimuli moving toward the head, and signals conveying auditory motion around the head in a regions of the intraparietal sulcus that is the putative human equivalent of the VIP region in monkeys (Colby and Duhamel, 1991; Duhamel et al., 1998; Avillac et al., 2007). This finding was extended by the studies of Sereno, Huang, and colleagues that described multisensory neuronal populations with visual and tactile receptive fields located on the head and in spatial alignment with each other (Sereno and Huang, 2006; Huang et al., 2012). More recently, two neuroimaging studies have corroborate the role of the putative human VIP in the processing of visual and tactile signals from the face (Cardini et al., 2011; Apps et al., 2013).

Similarly, a few neuroimaging studies have gathered evidence for the convergence of visual and tactile signals from the hand in fronto-parietal areas (Lloyd et al., 2003; Makin et al., 2007; Nakashita et al., 2008; Beauchamp et al., 2010; Longo et al., 2012b). Lloyd and colleagues identified brain regions where visual and tactile signals converge to represent the spatial location of the hand (Lloyd et al., 2003). However, the authors did not describe the responses to unisensory and multisensory stimuli to shed light on the nature of the integrative processes in these areas. Moreover, Beauchamp and others described how hand-related visual and tactile signals are processed in the posterior parietal cortices to facilitate detection and discrimination tasks (Saito et al., 2003; Nakashita et al., 2008; Beauchamp et al., 2010; Pasalar et al., 2010). Finally, Makin and colleagues provided additional evidence for the convergence of visual and tactile signals from the hand in a region of the anterior intraparietal cortex (Makin et al., 2007). However, the authors did not compare the responses to unisensory stimuli with those to multisensory stimuli, nor did they relate the BOLD responses to the sensory stimuli delivered to the hand to the self-perception of the upper limb.

The same neuroimaging study (Makin et al., 2007) was the first to attempt to provide evidence in favor of the existence of a representation of the perihand space in the human brain (Makin et al., 2007; see also Serino et al., 2011 for a study using TMS), and suggested that regions in the posterior parietal and premotor cortices exhibit BOLD responses that are selective to visual stimuli presented close to, as opposed to far from, the hand. However, the previous study did not provide evidence for a representation of near space that is anchored to the hand, i.e., remapped when the arm changes position in space, nor did it link multisensory processing in the perihand space to the self-perception of the hand. Another neuroimaging study revealed that the BOLD response profile in a region of the posterior parieto-occipital cortex is tuned to near viewing, i.e., shows a preference for visual stimuli viewed close to, as opposed to far from, the head (Quinlan and Culham, 2007). Moreover, two recent studies found that the same region in the superior parieto-occipital cortex displays BOLD responses selective to the visual presentation of objects within reach of the participants' hand (Gallivan et al., 2009, 2011). The neuroimaging research reviewed above provides encouraging support for the notion that multisensory processes analogous to those that have been described in non-human primates are associated with the combination of sensory signals from the body and the space around it. Yet, some outstanding questions remain open that motivated the neuroimaging studies presented in this thesis. What human brain areas, BOLD response profiles, and spatio-temporal principles underlie the integration of visual, tactile, and proprioceptive signals from the upper limb? Are multisensory neuronal populations in these areas equipped with hand-centered visual RFs restricted to the perihand space? Perhaps more importantly, how are these mechanisms related to the self-perception of the hand?

Valuable insights to the latter question are found in recent neuroimaging studies that have employed perceptual illusions to investigate the neural mechanisms of bodily self-perception (Tsakiris et al., 2010b; Blanke, 2012; Ehrsson, 2012). A seminal study by Ehrsson and colleagues adapted the rubber hand illusion paradigm (Botvinick and

Cohen, 1998) to a neuroimaging setting. This study revealed that the experience of ownership of an artificial hand is associated with increased activity in parts of the intraparietal, premotor, and cerebellar cortices (Ehrsson et al., 2004), and depends on the detection and integration of congruent visuo-tactile signals. Moreover, subsequent studies revealed that the embodiment of an artificial limb is mediated by multisensory processes that are not merely an effect of visual capture over touch and proprioception (Ehrsson et al., 2005), and is associated with emotional responses to threats directed toward the embodied artificial limb (Ehrsson et al., 2007; see also Lloyd et al., 2006). Furthermore, a positron emission tomography study of the rubber hand illusion emphasized the possible role of the posterior insular cortex in mediating the position sense of the upper limb (Tsakiris et al., 2007). The neuroimaging literature relating multisensory processes to bodily self-perception extends beyond the multiple experimental variations on the rubber hand illusion (Guterstam et al., 2013). In a recent study, we demonstrated that the self-attribution of a whole body is associated with the integration of congruent multisensory signals in the posterior parietal and premotor cortices and in the putamina (Petkova et al., 2011a). Furthermore, Ionta and colleagues identified a region in the bilateral superior temporal cortices whose BOLD responses reflect the subjectively reported spatial self-location of the body (Ionta et al., 2011b). Intriguingly, recent neuroimaging research also suggests that multisensory mechanisms may support the plastic self-perception of the face (Cardini et al., 2011; Apps et al., 2013). The multisensory literature summarized above has contributed to the large number of theoretical accounts reviewing the role of multisensory mechanisms in underpinning bodily self-attribution and self-location (Makin et al., 2008; Tsakiris, 2010; Aspell et al., 2012; Blanke, 2012; Ehrsson, 2012; Moseley et al., 2012; Apps and Tsakiris, 2013; Serino et al., 2013).

By synthesizing the evidence presented above, these theoretical models have put forward theoretical accounts describing how the human brain integrates information from all the sensory modalities, both exteroceptive and interoceptive, to support the construction and maintenance of a plastic and coherent representation of the bodily self. Despite the rich body of evidence they are built on, these models rely on a number of fundamental assumptions that are in need of experimental support (Botvinick, 2004; Moseley, 2011). Importantly, these assumptions trace back to the questions that were outlined when reviewing the evidence related to the multisensory integration of visual, tactile, and proprioceptive signals within a reference frame centered on a body and restricted to the peripersonal space. Specifically, multisensory models of bodily self-attribution attribute a pivotal role to visuo-tactile-proprioceptive integration in frontal, parietal, and subcortical areas. However, do these multisensory mechanisms underlie the integration of sensory signals from one's real body, or are they exclusive to the often unusual perceptual experiences associated with illusions of body ownership and self-location? Furthermore, the neuroimaging evidence for the existence of a body-part-centered representation of the peripersonal space, within which these multisensory mechanisms are thought to operate, is limited (Makin et al., 2007), and its link to the self-perception of the body remains unexplored. These considerations are indicative of the need of collecting neuroimaging evidence to substantiate the claims that form the bases for current models of bodily self-perception.

2.6 MULTISENSORY INTEGRATION AND PREDICTIVE CODING

The evidence reviewed above speaks in favor of the pivotal role that the integration of peripheral signals from the body and its surrounding space plays in the construction of a coherent representation of the body. Nevertheless, strong reasons exist to believe that the bottom-up integration of inter-related exteroceptive sensory information is not sufficient to produce a coherent sense of bodily self (Botvinick, 2004; Tsakiris, 2010; Moseley, 2011). Factors like the known visual appearance of the body (Tsakiris et al., 2010a; but see Guterstam et al., 2013), its morphological configuration (Ehrsson et al., 2004; Costantini and Haggard, 2007; Lloyd, 2007; Guterstam et al., 2011; Kalckert and Ehrsson, 2012), and its associated first-person perspective (Slater et al., 2009; Ionta et al., 2011b; Petkova et al., 2011a, 2011b) are illustrations of the significance of the interplay between incoming sensory signals and pre-existing higher-order implicit and explicit representations of the body (Cardinali et al., 2009a; Tsakiris et al., 2010a; Ionta et al., 2011a; Longo et al., 2012a; Apps and Tsakiris, 2013). Specifically, it remains to be explained how the brain interprets the incoming sensory information against the compilation of innate and acquired knowledge of the morphological, functional, and perceptual attributes of the body. A promising theoretical framework within which to pose and interpret these questions is offered by a unifying theory of perception known as predictive coding (Friston, 2009, 2010, 2013; Hohwy and Paton, 2010; Seth et al., 2011; den Ouden et al., 2012; Apps and Tsakiris, 2013; Clark, 2013; Limanowski and Blankenburg, 2013; Schwartenbeck et al., 2013).

The predictive coding account of the structural and functional organization of the brain's perceptual systems focuses on perception as a collection of active, rather than passive, inferential mechanisms. In a nutshell, these theories postulate that perceptual systems operate by continuously comparing predictions concerning incoming sensory information with the actual inputs (Friston, 2009, 2010, 2013). The former take the shape of *prediction* signals, generated dynamically by higher-order areas and fed back to lower-level areas, whereas the latter take the form of *prediction error* signals, fed forward from early areas to higher-order areas with information concerning the discrepancies between the predicted and the received inputs (Rao and Ballard, 1999; Friston, 2009; den Ouden et al., 2012; Clark, 2013). By iteratively adapting its predictive parameters, the brain aims at minimizing the difference between the predicted and the actual states of the environment, attaining a state of perceptual stability and coherence that is essential for behavior (Ernst and Bülthoff, 2004; Friston, 2010). A growing body of neuroimaging literature has gathered support for the role of predictions and prediction errors in perceptual mechanisms, focusing primarily on the visual (Summerfield et al., 2008; Egner et al., 2010; den Ouden et al., 2012; Kok et al., 2012; de Gardelle et al., 2013a, 2013b) and auditory (Garrido et al., 2008; Todorovic et al., 2011; Wacongne et al., 2011; Sanmiguel et al., 2013; Sanmiguel et al., 2013) modalities, whereas the neuroimaging evidence in favor of the existence and function of multisensory predictions remains meager.

How can the multisensory mechanisms of body self-perception reviewed above be contextualized within predictive coding theories of perception? Within this framework, interoceptive and exteroceptive afferent sensory information is combined with prior knowledge to maintain and update a coherent representation of the body. In order to promote stability and coherence, this representation is suitably plastic and can be updated to project the feeling of embodiment onto artificial limbs and whole bodies, as implied by the plethora of existing perceptual illusions of body ownership (Hohwy and Paton, 2010; Ehrsson, 2012; Apps and Tsakiris, 2013; Limanowski and Blankenburg, 2013). In turn, this central representation of the body allows specific sensory and motor predictions to be formulated with respect to the incoming sensory information and to the sensory consequences of one's own actions (Blakemore et al., 1998, 1999, 2000; Frith, 2012). A well-known example of the role of these self-specific predictions is the neural processing of the sensory stimulation generated by a self-produced action that results in the inability to "tickle oneself" (Blakemore et al., 1998, 1999, 2000). The significance of the proficiency to form accurate multisensory predictions concerning incoming sensory events is also evident with respect to one of the essential behavioral functions of the multisensory circuits that integrate information from the body and its surrounding space. Namely, the ability to protect the body from incoming threats identified through vision requires that somatosensory predictions be accurately formed concerning the body-centered location of the potential impact zone (Duhamel et al., 1998; Avillac et al., 2005). In turn, these multisensory predictions allow the planning and performance of appropriate motor sequences (Cooke and Graziano, 2003; Cooke et al., 2003; Sambo et al., 2012b; Sambo and Iannetti, 2013). Despite the theoretically relevant interpretation of the multisensory mechanisms of body self-perception within the framework of predictive coding, the question of how self-specific multisensory predictions contribute to the maintenance of a coherent representation of the body is in need of experimental support.

According to models that are centered on the interplay between the integration of afferent sensory signals from the hand and higher-order representations of the hand itself, the multisensory fronto-parietal areas generate predictions concerning incoming sensory signals. In order to be self-specifying, these predictions need to distinguish sensory information that is self-related, i.e., attributed to one's own hand, from sensory information that is not labeled as "self". However, this key tenet remains in need of experimental support. How can the existence of self-specific multisensory predictions be tested using neuroimaging? Again according to the models outlined above, the multisensory predictions generated by the higher-order representation of the hand are continuously compared to the afferent sensory inputs processed in the corresponding early sensory cortices. If an unpredictable discrepancy is detected between the expected and the afferent inputs, the early sensory cortices generate prediction error signals that higher-order areas can employ to dynamically update the multisensory expectations in light of changes in the sensory environment. Hence, the introduction of unexpected violations of these multisensory expectations and the measurement of the evoked neural responses would constitute an experimental probe for the existence of self-specifying multisensory predictions.

In order to test these ideas, it becomes essential to first gather evidence in favor of the basic mechanisms that support the construction of the central representation of the hand. In the experiments presented in the thesis, we sought to provide evidence for the convergence and integration of visual, tactile, and proprioceptive inputs from the upper limb in frontal, parietal, and subcortical human brain regions. The neuroanatomical hypotheses were grounded on the neurophysiological, behavioral, neuropsychological, and neuroimaging evidence reviewed above. Furthermore, we tested the hypothesis that these areas contain neuronal populations that are selective to the presence of an object in the immediate space around the hand. This finding would provide evidence for the existence of the hand-centered central representation of the perihand space. Then, we employed complementary neural, behavioral, and psychophysiological measures to relate the above mechanisms to the self-perception of the hand, focusing on the feeling of ownership and the sense of position of the upper limb. Finally, we capitalized on the evidence obtained from the preceding experiments to investigate the hypothesis that the central representation of the hand forms multisensory predictions concerning incoming sensory signals. In particular, we envisaged that these predictions would be unique to the self-attribution of the hand, and would reflect the self-specific neuronal processing of the sensory inputs to one's own hand.

2.7 SPECIFIC HYPOTHESES

The preceding sections brought together multiple scientific disciplines, including neurophysiology, neurology, psychology, and cognitive neuroscience, to synthesize the evidence in favor of the existence of a central multisensory representation of the hand and the space around it. Furthermore, the above evidence supports the notion that this dynamic multisensory representation of the hand is related to the self-perception of the upper limb. A number of outstanding open questions were identified, establishing a background for the hypotheses that motivated the experiments presented in this thesis. The overarching hypotheses can be formulated as follows:

(1) Frontal, parietal, and subcortical human brain regions integrate visual, tactile, and proprioceptive signals from one's own hand to construct and maintain a coherent representation of the upper limb in space;

(2) This multisensory representation of the hand is associated with a selective representation of the space around it, the perihand space, that encodes visual stimuli in hand-centered coordinates;

(3) The multisensory representation of the hand and the perihand space is related to the self-perception of the hand, that depends on the congruence of the sensory inputs to the upper limb;

(4) The self-perception of the hand is also associated with the dynamic formation of multisensory predictions that reflect the self-specific neuronal processing of the sensory inputs to one’s hand.

3 AIMS

The foremost objective motivating the studies presented in this thesis was twofold: (1) to characterize the neural correlates of the integration of multisensory signals from the hand, and (2) to provide evidence for the existence of a central representation of the space around the hand in the human brain. The overarching purpose was to attempt to relate the above mechanisms to the neural and psychological phenomena associated with the self-attribution of the hand. The following list contains a brief overview of the aims specific to each of the studies included in the thesis:

I. **Study I** was aimed at characterizing the BOLD responses to visual, tactile, and combined visuo-tactile stimuli delivered to one's own right hand. By analyzing the BOLD responses to unisensory and multisensory stimuli, we identified candidate cortical and subcortical areas that perform the integration of these sensory signals.

II. **Study II** was designed to characterize the integration of multisensory signals from the hand by manipulating their spatio-temporal congruence. This study also explored the relationship between the multisensory representation of the hand and the hand's self-attribution, employing neural, subjective, and psychophysiological measures.

III. **Study III** was designed to provide neuroimaging evidence for the existence of a selective representation of the perihand space in frontal, parietal, and subcortical regions of the human brain.

IV. **Study IV** examined the hand-centered spatial properties of the central representation of the perihand space and its relationship with the feeling of ownership and the position sense of the hand.

V. **Study V** tested the hypothesis that the coherent central representation of the hand is associated with the formation of self-specific predictions concerning upcoming stimuli from multiple sensory modalities.

4 METHODOLOGICAL CONSIDERATIONS

The aim of this section is to provide an overview of the experimental procedures associated with the studies featured in the thesis. The methodological procedures are introduced together with a description of the rationale behind their choice and a critical discussion of their advantages and inherent limitations. For a detailed description, the reader is referred to the full version of the corresponding article or manuscript.

4.1 PARTICIPANTS AND ETHICAL CONSIDERATIONS

All of the participants were healthy human volunteers, recruited primarily through advertising the experiments among the student population in the Stockholm region. The participants had normal or corrected-to-normal vision and no history of neurological, psychiatric, or sensory disorders, and received monetary compensation for their participation. The participants' handedness was logged through self-reports. The experiments were performed in accordance to the highest ethical standards for research involving healthy human volunteers. The Ethical Review Board of Stockholm approved the experiments, and the participants provided their written informed consent prior to taking part in the studies. The volunteers were screened to ensure total safety in their participation in the fMRI scanning session and were given a detailed description of the experimental setup and relevant instructions about the study. A total of 24 participants took part in **Study I** (5 females, mean age ± standard deviation, 25±4 years), 30 in **Study II** (15 in Experiment 1, 4 females, 27±3 years; 15 in Experiments 2 and 3, 5 of whom had taken part in Experiment 1; 5 females, 26±3 years), 22 in **Study III** (5 females, 26±5 years), 42 in **Study IV** (26 in Experiment 1, 4 females, 29±6 years; 16 in Experiment 2, 9 of whom had taken part in Experiment 1; 5 females, 31±8 years), and 23 in **Study V** (11 females, 27±5 years).

4.2 FUNCTIONAL MAGNETIC RESONANCE IMAGING

The common thread between all the studies in the thesis is the use of the neuroimaging technique known as functional magnetic resonance imaging (fMRI). In 2003, Paul Lauterbur and Peter Mansfield were awarded the Nobel Prize in Physiology or Medicine for their discoveries concerning MRI, a technique that has revolutionized clinical practice around the world. It was with the introduction of a new image contrast, termed Blood Oxygenation Level Dependent (BOLD; Ogawa et al., 1990; Kwang et al., 1992; Logothetis et al., 2001), that the use of MRI for functional brain imaging gained substantial momentum, setting off an era of technological developments that has turned fMRI into a pillar of modern cognitive neuroscience. A simple query using the single keyword *fmri* on PubMed (US National Library of Medicine, National Institutes of Health, USA; *http://www.ncbi.nlm.nih.gov/pubmed/?term=fmri*), performed on October 30th, 2013, yielded over 340k hits.

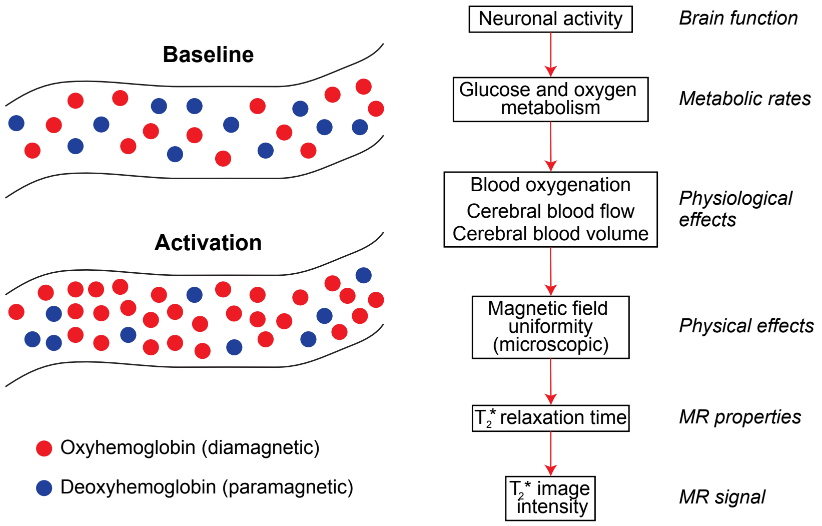

Figure 1. The neurophysiological origins of the BOLD signal are a cascade of complex events that map dynamic changes in brain function to variations in the image intensity of MRI scans.

The BOLD image contrast, as the name implies, arises from the different magnetic properties ascribed to oxygenated and deoxygenated blood. Through a complex and not yet fully understood chain of events, dynamic changes in neuronal activity trigger a cascade of metabolic and physiological effects that result in changes in blood flow, volume, and oxygenation in the vicinity of the active neuronal populations. Because changes in blood oxygenation have an impact on the uniformity of the local magnetic field surrounding the active neuronal populations, the MRI signal measured by the scanner changes as a consequence of brain activity. Thus, a connection is established between dynamic changes in neuronal activity and temporal variations in the MRI signal that accounts for the term *functional* in fMRI. This overly simplified description of the neurophysiological mechanisms underlying the BOLD image contrast, together with the astounding success of fMRI in cognitive neuroscience, belies the sheer complexity of the technique and begs for a critical evaluation of its benefits and pitfalls.

4.3 BENEFITS AND PITFALLS WITH THE USE OF FMRI

The paramount benefit with the use of fMRI in neuroscience rests with its ability to non-invasively monitor changes in brain activity as healthy and diseased animals (from rodents to non-human primates and humans) receive sensory stimuli or engage in behavioral and cognitive tasks. The possibility to capture fluctuations in activity across the whole brain, with relatively high spatial specificity, and relate them to ongoing behavior offers a unique tool to investigate the functional organization of the human brain. Despite these evident benefits, a number of limitations are inherent to the use of fMRI and must be kept in mind when designing experiments and interpreting the findings. Arguably, the most important drawback with fMRI is its intrinsically indirect and correlative nature. The complex chain of events that links changes in neuronal activity to variations in the BOLD image contrast renders the findings obtained with fMRI an *indirect* measurement of brain function, the latter essentially being defined as the electrical activity of individual neurons and the circuits they form. Furthermore, the BOLD signal measured across the brain provides only a *correlative* panorama of the neuronal activity associated with a specific function, making any inference on the *causal* role of brain areas inconclusive, unless coupled with complementary techniques such as transcranial magnetic stimulation, neurological studies, pharmacological interventions, and so forth. A second drawback with the use of fMRI worth mentioning here is its inherent boundaries in spatio-temporal resolution. First, the BOLD signal associated with a spatial unit of functional MRI data, or voxel, reflects the contribution of hundreds of thousands, if not more, individual neurons, curtailing the inferential power on the role of single neurons and local microcircuits. Nevertheless, numerous developments in both hardware (for instance, the potential for ultra-high spatial resolution with increasing field strength) and analysis methods (such as BOLD-adaptation – see Studies II and III – and multivariate pattern analysis; see Petkova et al., 2011a) have been boosting the spatial sensitivity of fMRI, as evident from the progress in reliably identifying complex structures such as cortical columns, thought to be a widespread principle of brain organization (Yacoub et al., 2008). Second, the time required to collect a full volume of data, ranging in most current studies from 2 to 3 seconds, limits the temporal resolution of fMRI. Hence, the description of the temporal dynamics of brain function obtained with fMRI is restricted to a time domain that is several orders of magnitude wider than that associated with the electrophysiological activity of neurons and microcircuits (Logothetis, 2008).

Despite the intrinsic limitations briefly reviewed here, the perks with the use of fMRI remain vast. With respect to the work described in this thesis, two main advantages come to mind: (1) the possibility to non-invasively and reliably map the functional properties of regions of the human brain related to specific mechanisms, such as the integration of sensory signals from the body and the representation of the space around it, and, perhaps even more importantly, (2) the potential to investigate the link between brain responses in behaving humans and particular aspects of complex psychological phenomena, such as the self-attribution of the hand.

4.4 CHARACTERIZING MULTISENSORY INTEGRATION USING FMRI

The seminal studies that propelled the development of research on the integration of the senses were neurophysiological investigations performed on cats and non-human primates (Rizzolatti et al., 1981a, 1981b; Graziano and Botvinick, 2002; Stein and Stanford, 2008). These studies benefited from the opportunity to record the electrical activity of individual neurons exposed to stimuli from multiple sensory modalities, and led to the development of the fundamental principles of multisensory integration that are still central to modern psychological and neuroscientific research in humans (Driver and Noesselt, 2008; Stein and Stanford, 2008; Noppeney, 2012). The advent of non-invasive neuroimaging techniques like fMRI spurred an ongoing era of studies attempting to characterize multisensory integration in behaving humans (Calvert et al., 2000, 2001). Indeed, one of the aims of the present thesis was to provide evidence for the existence of multisensory integrative processes concerning the sensory signals from the hand. Because of the inherent limitations of human neuroimaging discussed previously, the extension of the basic neurophysiological principles to fMRI is far from straightforward (Calvert and Thesen, 2004; Beauchamp, 2005; Laurienti et al., 2005; Goebel and van Atteveldt, 2009; Stevenson et al., 2009; Noppeney, 2012).

Among the criteria that have been put forward in neuroimaging investigations of multisensory integration, the most direct involves the comparison of the BOLD response to a multisensory stimulus to the responses to unisensory stimuli presented in isolation. The corresponding statistical criteria applied to the multisensory BOLD responses vary in their stringency and inferential power. A graphic summary of some of these criteria is presented in Figure 2A.

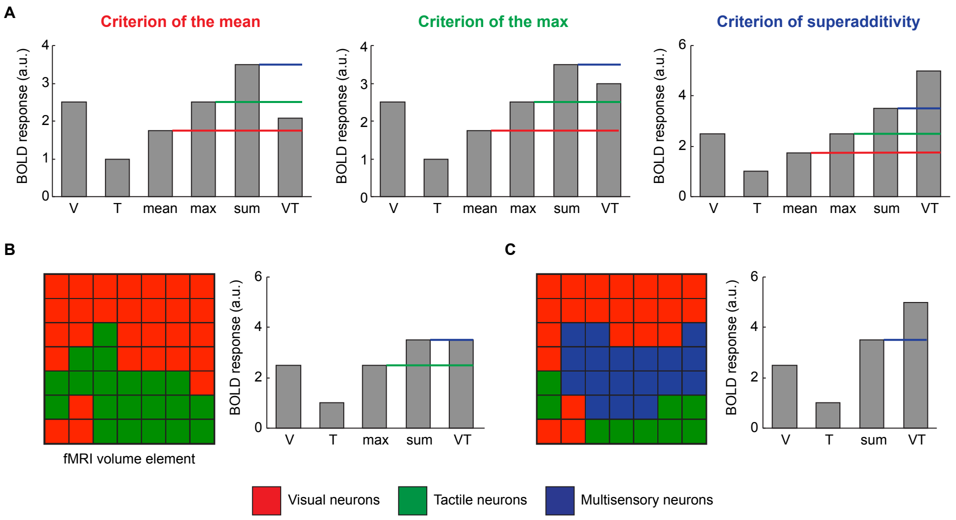

Figure 2. (**A**) Overview of some of the statistical criteria employed to characterize multisensory BOLD responses. The bar charts display the responses of a sample voxel to visual (V) stimuli, tactile (T) stimuli, and combined visuo-tactile (VT) stimuli, together with their mean, the maximum of the unisensory responses, and their sum. (**B**) A sample voxel containing separate non-interacting visual and tactile neurons. (**C**) A non-linear superadditive response to VT stimuli strongly suggests that the voxel contains multisensory neurons that integrate the unisensory signals.

The criterion of the mean, for example, classifies a BOLD response as multisensory if greater than the average of the responses to the unisensory stimuli, whereas the criterion of the maximum takes into account the most responsive unisensory condition. Both constitute examples of a subadditive BOLD signal, a response profile whose analogous in neurophysiology belongs to the range of the observed responses to multisensory stimuli (Laurienti et al., 2005; Avillac et al., 2007; Stein and Stanford, 2008). However, given the spatial resolution of fMRI data, where an individual voxel contains hundreds of thousands or more neurons, these response profiles cannot be disentangled from the case of a voxel that contains populations of non-interacting modality-specific neurons (Figure 2B). The most conservative of these basic criteria, the criterion of superadditivity, relies instead on a significant difference between the BOLD response to the multisensory condition and the sum of the responses to the unisensory conditions (Figure 2A). If the criterion is met, a strong argument can be made in favor of the existence of multisensory neuronal populations within the voxel (Figure 2B), whose non-linear response profile cannot be accounted for by the existence of non-interacting modality-specific neurons. Instead, a non-linear interaction between the sensory inputs is necessary to elicit a superadditive response, be it at the level of neuronal firing rates or synaptic activity (Logothetis et al., 2001; Logothetis, 2008). In light of this, the superadditivity criterion arguably ranks first in terms of inferential power, and has successfully been adopted in several neuroimaging studies of multisensory integration (Calvert et al., 2001; Ehrsson et al., 2004; Stevenson et al., 2007; Werner and Noppeney, 2010, 2011; Petkova et al., 2011a; Tubaldi et al., 2011; Tyll et al., 2013). Nevertheless, a number of caveats must be taken into account when interpreting the results of the application of the superadditivity criterion to BOLD fMRI. Some of these factors trace back to the neurophysiological principles of multisensory integration, whereas others are intrinsic to the use of fMRI. First, superadditivity is not the only operational profile of multisensory neurons, and computations that are subadditive or linear in nature have been observed consistently and deemed relevant for neuronal processing and behavior (Laurienti et al., 2005; Stanford and Stein, 2007). Second, the occurrence of superadditive responses may vary based on the efficacy of the unisensory stimuli, a phenomenon that has been termed the *principle of inverse effectiveness* (Holmes and Spence, 2005a; Stein and Stanford, 2008; Noppeney, 2012). In other words, the benefit of a non-linear combination of the sensory inputs may decrease with the increased effectiveness (neuronal and behavioral) of the unisensory signals. Third, the superadditivity criterion is likely to increase the incidence of false negatives in fMRI analyses because of the complex physiological dynamics underlying the BOLD signal, such as vascular ceiling effects (Buxton et al., 2004). All of the above factors contribute to making the superadditive criterion perhaps too conservative, and certainly not exhaustive. Nevertheless, the detection of a non-linear BOLD response represents very strong evidence in favor of the existence of multisensory processes, and is particularly powerful, for instance, when applied in the context of well controlled factorial experimental designs (Ehrsson et al., 2004; Tsakiris et al., 2007; Petkova et al., 2011a). In summary, the selection of the statistical criteria to evaluate BOLD responses to multisensory stimuli can have a large impact on the interpretation of the findings, and must always be kept in mind when presenting and discussing the findings (Beauchamp, 2005; Holmes and Spence, 2005a; Laurienti et al., 2005; Goebel and van Atteveldt, 2009; Stevenson et al., 2009; Noppeney, 2012).

Numerous other analysis techniques have been developed to address the issue of multisensory integration in fMRI. Worth mentioning here are the use of BOLD-adaptation paradigms (see next section), which tap into the sub-voxel selectivity profile of neuronal populations, and the manipulation of the congruence (spatial, temporal, semantic, etc.) of the stimuli (Calvert et al., 2001; Macaluso and Driver, 2005; Noesselt et al., 2007; Noppeney, 2012). The latter has the advantage to restrict statistical comparisons to multisensory conditions, overcoming some of the limitations typical of the criteria reviewed above. Congruence manipulations have been key to numerous neuroimaging investigations of the multisensory mechanisms underpinning the sense of body ownership (Ehrsson et al., 2004, 2005, 2007; Tsakiris et al., 2007, 2010b; Ionta et al., 2011b; Petkova et al., 2011a; Longo et al., 2012b; Guterstam et al., 2013). However, the effects of the manipulation of multisensory congruence can be dependent upon the cognitive and attentive state of the participant, the type and predictability of the stimuli used, and on the task (if any) the participant is engaged in during the experiment (Corbetta and Shulman, 2002; Zimmer and Macaluso, 2007; Talsma et al., 2010; Noppeney, 2012). In conclusion, the characterization of multisensory integrative processes using fMRI demands careful considerations, particularly when selecting the stimuli, defining the experimental design, and selecting the statistical criteria to evaluate the BOLD responses to the multisensory conditions.

4.5 BOLD-ADAPTATION: MAKING STRONGER INFERENCES ON NEURONAL SELECTIVITY

Recent developments in fMRI analysis methods have boosted the sensitivity to detect effects that may otherwise elude conventional analysis techniques. One such method that has proven particularly fruitful is BOLD-adaptation, also known as fMRI-adaptation or repetition suppression (Grill-Spector and Malach, 2001; Avidan et al., 2002; Krekelberg et al., 2006; Weigelt et al., 2008; Malach, 2012; Davis and Poldrack, 2013). The use of BOLD-adaptation is predicated on the neurophysiological phenomenon of neural adaptation, whereby the responsiveness of single neurons selective to particular stimulus features declines with the continued repetition of those features (Li et al., 1993; Miller et al., 1993; Miller and Desimone, 1994; Sobotka and Ringo, 1996; Sawamura et al., 2006). This basic principle has been successfully extrapolated to the analysis of the BOLD signal, where it enhances the sensitivity to make inferences on the selectivity of neuronal populations to a widespread range of neural processes, such as the encoding of object properties (Grill-Spector et al., 1999; Sayres and Grill-Spector, 2006; Tal and Amedi, 2009), processing of object attributes for reaching and grasping (Rice et al., 2007; Króliczak et al., 2008; Bernier and Grafton, 2010; Monaco et al., 2011), spatial representations (Doeller et al., 2010), tool use (Valyear et al., 2012), audio-visual integration (Doehrmann et al., 2010; van Atteveldt et al., 2010), processing of faces (Loffler et al., 2005), representation of abstract events (Schapiro et al., 2013), language (Menenti et al., 2012) and so forth. By tapping into the selectivity profile of neuronal populations likely to be intermingled within a single fMRI voxel with neurons with different response properties, BOLD-adaptation has been described as attaining sub-voxel resolution (Grill-Spector, 2006; Malach, 2012). However, the intrinsic complexity of the neural adaptation phenomenon, exacerbated by the complex and not yet fully understood dynamics underlying the emergence of the BOLD response, requires that caution be exercised when drawing inferences from BOLD-adaptation analyses (Krekelberg et al., 2006; Sawamura et al., 2006; Summerfield et al., 2008; Larsson and Smith, 2012). In particular, different models have been proposed that account for the neurophysiological mechanisms underpinning the BOLD-adaptation effect (Grill-Spector et al., 2006; Epstein et al., 2008). For instance, the repeated presentation of a stimulus can lead to (1) fatigue effects on neuronal processing, (2) sharpening of the neuronal population response, with fewer neurons being recruited, and/or (3) facilitation of neuronal processing, requiring less temporal and metabolic resources. These different models would all account for the decrease in the neuronal response to the repeated presentation of a stimulus that underpins the use of BOLD-adaptation (Grill-Spector et al., 2006). Furthermore, the experimental observation of the opposite phenomenon, indicated as *repetition enhancement*, in conjunction with or instead of repetition suppression, clarifies that the basic principles underlying BOLD-adaptation may not apply, or at least not exclusively, to the processing of repeated stimuli and cognitive tasks (de Gardelle et al., 2013a, 2013b; Segaert et al., 2013).

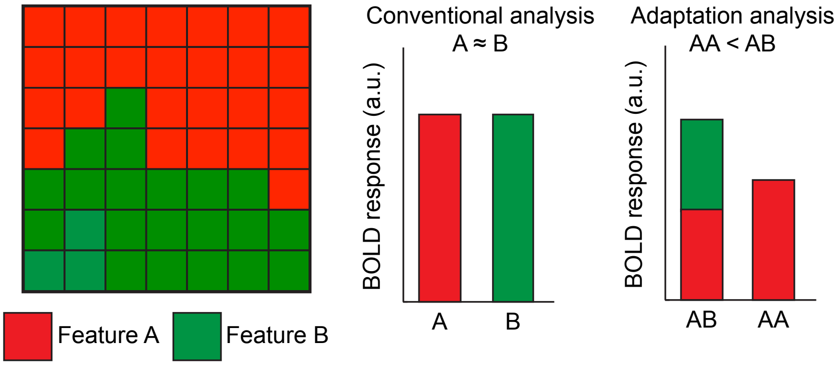

Figure 3. Overview of the logic behind the use of BOLD-adaptation. If a sample voxel contains two distinct neuronal populations sensitive to two different types of stimuli, the direct comparison of the BOLD responses evoked by the presentation of the two stimuli has little inferential power on neuronal selectivity. In an adaptation analysis, on the other hand, the repetition of the stimulus feature of interest enhances the statistical power to detect the existence of neuronal populations tuned to that feature.

The above considerations recommend caution when interpreting the findings from BOLD-adaptation studies. Nevertheless, the use of these paradigms has been validated in many domains of cognitive neuroscience and provides the possibility to overcome some of the limitations imposed by the spatial resolution of fMRI data on conventional analysis techniques (Figure 3). In the following, the discussion focuses on the rationale and the advantages associated with the employment of BOLD-adaptation in the investigation of the mechanisms underlying the representation of the perihand space in the human brain.

The use of BOLD-adaptation proved to be particularly well suited to the exploration of one of the key hypotheses motivating the work described in this thesis. In **Studies III** and **IV**, we set out to gather evidence for the existence of neuronal populations in the human brain that construct a hand-centered representation of the space around the hand (*perihand space*). To achieve this goal, we experimentally tapped into one of the fundamental properties of such neuronal populations, well documented by research in non-human primates: visual receptive fields (*RFs*) restricted to the space immediately surrounding the hand, and anchored to the hand when the upper limb changes position in space (Graziano, 1999; Graziano et al., 2000). Accordingly, we needed to demonstrate (1) the selectivity of these neuronal populations to visual stimuli presented close to, as opposed to far from, the hand, and (2) the spatial remapping of the visual RFs as the hand changes position in space. Because neuronal populations with these properties may be intermingled with neurons selective to different stimulus features (such as eye-centered RFs, body-centered RFs, motion selectivity, etc.), conventional analyses might not be sensitive enough to detect their existence (Grill-Spector and Malach, 2001; Malach, 2012; but see Makin et al., 2007). Hence, we designed BOLD-adaptation paradigms where the stimulus features changed along the desired dimension, i.e., the relative position of a three-dimensional object with respect to the participants' right hand. We were then able to formulate a straightforward prediction: if neuronal populations exist that respond selectively to an object presented close to the hand, then stronger BOLD-adaptation is expected if the object is repeatedly presented in the vicinity of the hand, as opposed to far from it. This approach controls for the selectivity to a number of stimulus features, such as motion, retinotopic or spatiotopic coordinates, low-level visual features, etc., and returns evidence for the existence of neuronal populations selective to an object presented close to the hand, possibly at the level of sub-voxel resolution.

The decision to employ BOLD-adaptation to probe the existence of a representation of the perihand space in the human brain was further supported by the observations reported by researchers investigating similar mechanisms in monkeys. Interestingly, the neurophysiological work of both Rizzolatti and colleagues (Rizzolatti et al., 1981a) and Graziano and colleagues (personal communication) remarked on the tendency of perihand neurons to adapt (i.e., decrease their firing rate) to the repeated presentation of an object in the vicinity of the upper limb. These observations reinforced our estimates concerning the aptness of the use of BOLD-adaptation to identify neuronal populations sensitive to visual stimuli within the perihand space.

In summary, we capitalized on the potential offered by BOLD-adaptation to identify neuronal populations with distinct selectivity to the stimulus feature that best fitted our hypothesis, i.e., the relative location of an object with respect to the hand. In turn, this led to stronger inferences concerning the existence of a representation of the perihand space in the human brain, adding to plentiful neurophysiological data and more recent behavioral and neuropsychological observations in humans.

4.6 FUNCTIONAL MRI DATA ACQUISITION AND PREPROCESSING

All of the fMRI data presented in this thesis were acquired using the Siemens TIM Trio 3T scanner located at the Karolinska University Hospital in Huddinge, Sweden. An appropriate acquisition protocol was set up for each study, offering coverage of the whole brain, a spatial resolution of 3 mm isotropic, and a temporal resolution of 2.5-3 seconds. Suitable tests were carried out prior to the onset of each study to ensure that the image quality would not be affected by the introduction of specific hardware components, such as MR-compatible head mounted displays, eye-tracking cameras, or force sensors, and to minimize the effects generated by movement, both of the participants' head and of the experimenters delivering visual and tactile stimuli inside the MRI scanner. Specific hardware modules were deemed compatible with the experimental setup if the relative increase in background noise associated with their usage did not exceed 5%. The participants were extensively reminded about the importance of minimizing head movements, and further precautions were taken in this direction by using foam pads to stabilize the participant's head. The fMRI data were screened for potential issues with image quality both by visual inspection and with the help of image analysis tools such as the ART toolbox (Massachusetts Institute of Technology, Cambridge, MA, USA). No datasets were discarded because of problems with the quality of the images. Prior to any statistical analysis, the fMRI data underwent a series of spatio-temporal preprocessing steps. The software used for these analyses was the version 8 of SPM (Statistical Parametric Mapping, Wellcome Center for Neuroimaging, University College London, UK), in conjunction with custom-made Matlab (The MathWorks Inc., Natick, MA, USA) scripts.

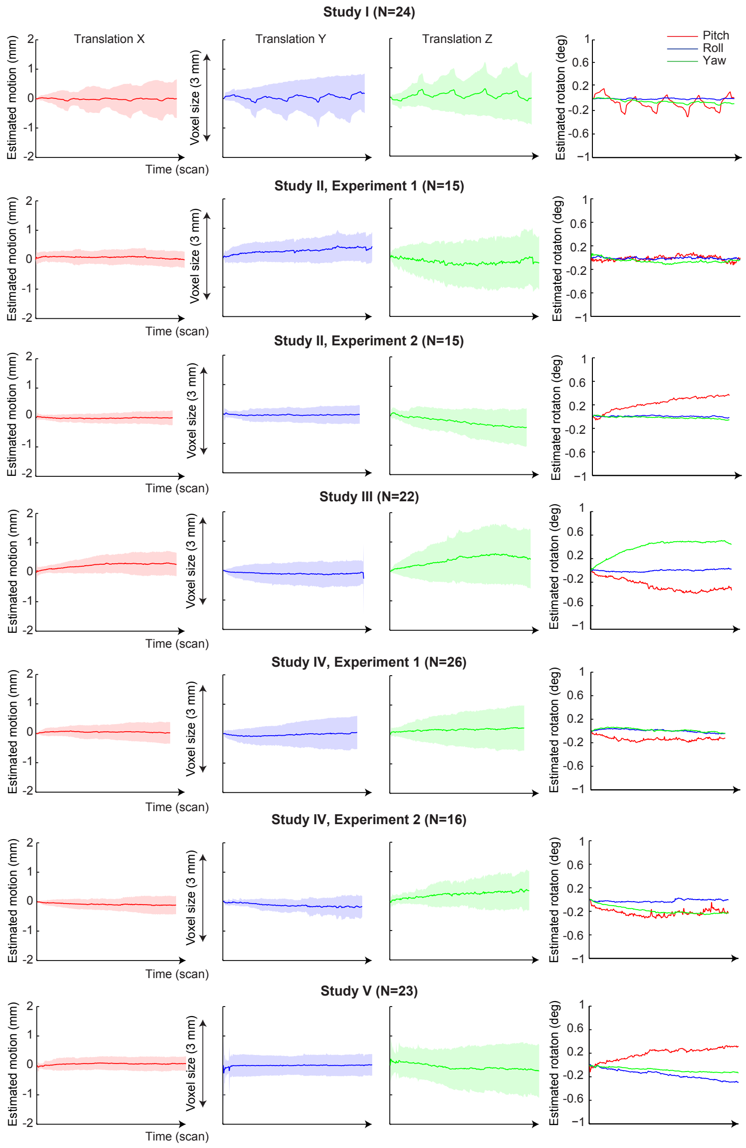

Figure 4. Average estimated realignment parameters for all the participants in all the experiments presented in the thesis. The average translations in the x, y, and z direction were always well within the illustrative margin of the voxel size. The six realignment parameters were added as regressors of no interest in the first-level general linear models to account for residual effects of head motion.

In brief, the fMRI data were realigned in space to compensate for head movements, and interpolated in time to account for inter-volume differences in acquisition time. The motion corrected data were scrutinized for excessive head motion, and six linear regressors containing the realignment parameters (translation in the x, y, and z directions, as well as the estimated changes in the pitch, roll, and yaw angles over time) were added to the first-level general linear model for each participant. As a reference, special attention was paid to abrupt head movements (as opposed to slow, monotonic variations), and translations that were of comparable extent to, or exceeding, the size of the image voxels (3 mm isotropic in all experiments). As displayed in Figure 4, the average estimated head motion parameters (relative to the reference scan) across all the experimental sessions were within the margin defined by the voxel size. The realignment regressors accounted for the variance in the data related to the residual effects of head motion in the datasets. The functional data were co-registered with a high-resolution structural scan of the participant's brain and normalized to a standard space (the MNI template, Montreal Neurological Institute, Canada) to enable group analyses and inter-study comparisons. Finally, the fMRI data were spatially smoothed with a Gaussian filter with a full-width-at-half-maximum of 8 mm isotropic, a passage that helps lessen the impact of inter-individual anatomical variability and conforms to the requirements of random field theory, the theoretical framework underlying the computations required to build statistical parametric maps of fMRI data (Friston, 2007).

4.7 GENERAL LINEAR MODELS FOR THE ANALYSIS OF FMRI DATA

The fMRI data from all the studies in the thesis were analyzed by building standard univariate general linear models including the experimental conditions of interest, the appropriate nuisance regressors (such as motion correction parameters), and behavioral covariates (such as subjective ratings or physiological responses). All the regressors in the model were defined based on the onset time and duration of each condition. The synchronization of the different stimulus presentation tools and data acquisitions devices with the MRI scanner guaranteed the accuracy of the timing information. To account for the temporal lag of the hemodynamic response, the regressors in the general linear model were convolved in time with the standard hemodynamic response function implemented in SPM8. The corresponding statistical model for each experiment was therefore a massively univariate general linear model defined for each voxel in the brain volume, recapped by the following equation:

$$\boldsymbol{Y} = \boldsymbol{X}\beta + \boldsymbol{E}$$

where $\boldsymbol{Y}$ contains each voxel's time series, $\boldsymbol{X}$ is the *design matrix*, β contains the regressor parameters to be estimated, and E contains the error terms, assumed to be Gaussian, independent, and identically distributed. A process that minimizes the sum of the squared error terms was used to yield the model parameter estimates:

$$\beta_{model} = (\boldsymbol{X}^{\mathrm{T}} \boldsymbol{X})^{-1} \boldsymbol{X}^{\mathrm{T}} \boldsymbol{Y}$$

for each voxel in the brain volume and each regressor in the design matrix. The estimated model parameters were combined linearly to form contrasts of interest:

$$[c_1\ c_2\ \ldots\ c_{\mathrm{p}}]\ \beta_{model} = c^{\mathrm{T}}\ \beta_{model}$$

where c_i represents the contrast weight for the *i-th* regressor included in the linear contrast. The T statistics were then derived for each voxel b taking into account the variance associated with the contrast and the corresponding p values were used for significance testing. The experimental procedures behind the statistical inference for fMRI data are complex and deserve a critical discussion in the following.

4.8 STATISTICAL INFERENCE AND CORRECTIONS FOR MULTIPLE COMPARISONS

Statistical parametric maps encompassing the whole brain follow from the application of massively univariate linear models to each volume element (voxel) in the fMRI dataset. As a consequence, univariate statistical inference typically involves a very large number of tests (typically student-T tests), applied separately to each voxel. In other words, the hypothesis testing procedures associated with a specific linear contrast are carried out independently and in parallel for each voxel in the fMRI dataset. Hence, a sizable multiple comparisons problem emerges that calls for appropriate corrections to substantiate the inferences drawn from the analysis. Without a correction for multiple comparisons, the incidence of false positives (or type I errors), i.e., voxels invalidly labeled as active with respect to the contrast of interest, would severely undermine the validity of the conclusions (Friston, 2007; Bennett et al., 2009; Poldrack, 2012). As a reference, in an fMRI dataset comprising ≈100k voxels, a statistical parametric map with $\alpha=5\%$ would contain ≈5k false positives. With respect to univariate fMRI analysis, two main strategies to correct for multiple comparisons have been refined in recent years and implemented in analysis packages such as SPM: family-wise error rate corrections and false discovery rate corrections.

Family-wise error (FWE) rate statistical corrections are in keeping with the Bonferroni correction for multiple statistical tests, whereby the significance level for each individual test is set to α/n, where n is the total number of tests performed (Nichols and Hayasaka, 2003). Consequently, the probability of one or more false positive out of n tests equals α. Given the spatial auto-correlation of fMRI data – a consequence of both the intrinsic nature of the data and the spatial preprocessing – the number of independent tests performed does not simply equal the number of voxels in the dataset. Rather, FWE corrections implemented within the framework or random field theory take into account the spatial smoothness of the data and reflect the number of independent resolution elements (or *resels*) in the dataset, typically much smaller than the total number of voxels (Worsley et al., 1996; Poline et al., 1997; Friston, 2007). In a representative dataset included in this thesis, a total of ≈170k voxels resampled to a size of 2 mm isotropic and spatially smoothed by a Gaussian filter with FWHM 8 mm isotropic, yields ≈820 resels. Univariate hypothesis testing and the FWE corrections recapped above can be applied either to individual voxels (peak statistics) or to groups of voxels (*cluster* statistics). While being the most rigorous approach to tackle the multiple comparisons problem, whole-brain FWE corrections can be overly conservative and result in a high rate of false negatives (or type II errors, i.e., voxels invalidly labeled as non active with respect to the contrast of interest) and reduced statistical power. This can often be mitigated by appropriately combining *a priori* hypotheses on the expected neuroanatomical correlates of the effects of interest with the required corrections for multiple comparisons. To avoid biases and statistical circularities (Kriegeskorte et al., 2009; Poldrack and Mumford, 2009; Poldrack, 2012; Vul and Pashler, 2012), regions of interest can be identified by (1) fully orthogonal contrasts from the same dataset, (2) peaks of activation from other relevant studies and, (3) anatomical segmentation (manual, automated, or atlas-based) of cortical and subcortical regions (Friston et al., 2006; Saxe et al., 2006; Poldrack, 2007). The ensuing statistical *small volume corrections* (SVC), or corrections for multiple comparisons restricted to a region of interest or to a volume of voxels centered around a relevant location, lead to an increase in statistical power that reflects the advantage of well formulated *a priori* hypotheses. All the studies presented in this thesis were hypothesisdriven. As a result, specific predictions on the neuroanatomical correlates of the effects of interest could be formulated and employed to increase statistical power. Thus, small volume corrections for multiple comparisons were applied by taking into account either an orthogonal contrast from the same dataset or the coordinates of several peaks of activation from other relevant studies. SVCs were performed across all the voxels contained in a 6-10 mm diameter sphere centered on the relevant peak. This procedure was applied to all the statistical parametric maps for both linear contrasts and multiple regression analyses and ensured that all the statistical tests were unbiased and not circular.

An alternative method to correct for multiple comparisons in whole brain activation maps rests on the control of the false discovery rate (Benjamini and Hochberg, 1995). FDR corrections result in a proportion α of false negatives, leading to a less conservative correction than FWE methods and increased statistical power. In all the studies featured in this thesis, we inspected the whole brain activation maps for peaks of activations that passed the significance threshold set by the topological (related to the activation peaks) FDR implemented in SPM (Genovese et al., 2002; Chumbley et al., 2010). This ensured that the whole brain activation maps would be fully accounted for, including potentially significant results that were not expressed in the *a priori* hypotheses. For all the predicted effects, small volume corrections for multiple comparisons were performed according to the procedure described above. In conclusion, all the reported datasets were analyzed following established procedures and the rigorous application of statistical inference methods for fMRI data.

4.9 EXPERIMENTAL SETUPS: STRIVING FOR IMPROVED ECOLOGICAL VALIDITY

The spatial and technological constraints imposed by the MRI scanner often hamper attempts to design experiments that attain a sufficiently high level of ecological validity. As a result, the general validity of the conclusions drawn from the data can be limited by the nature of the experimental setups. These considerations strike as particularly apt when considering fMRI experiments including basic sensory stimuli or motor tasks. For instance, the investigation of the sensorimotor mechanisms that guide reaching and grasping hand actions requires that appropriate experimental setups be constructed to replace simulated and computer-based tasks with real-world movements with superior ecological validity (Quinlan and Culham, 2007; Gallivan et al., 2009, 2011; Bernier and Grafton, 2010; Cavina-Pratesi et al., 2010; Monaco et al., 2011; Snow et al., 2011). Similarly, the delivery of naturalistic visual and/or tactile stimuli to the participants in the MRI scanner represents a methodological challenge when keeping ecological validity in mind. In light of the above, we endeavored to adopt experimental setups offering the best possible compromise between stimuli that elicit robust BOLD responses and the overall ecological validity of the setup.

In all the studies presented in the thesis, visual and tactile stimuli were delivered to the participants' right hand using a realistic three-dimensional object. In **Studies I**, **III**, and **IV**, the participants' head was tilted forward to allow them to look directly at their hand, which was placed on a custom-made inclined support, and at the visual and tactile stimuli (Figure 5). This arrangement allowed us to bypass the use of stimuli with a weaker degree of ecological validity, such as visual stimuli presented on a computer screen and/or viewed indirectly via a mirror (Bremmer et al., 2001; Makin et al., 2007; Beauchamp et al., 2010), and tactile stimuli delivered via piezoelectric stimulators or air puffs (Macaluso et al., 2000; Sereno and Huang, 2006; Huang et al., 2012; Takahashi et al., 2013). The overall ecological validity of the setups was further increased by having the participants look directly at their hand and at the three-dimensional object moving in the vicinity of the hand and/or touching it (see for example Gallivan et al., 2009; Snow et al., 2011). Numerous pilot experiments, as well as all the key results, revealed that these stimuli induced robust and reliable BOLD responses in the majority of the participants. In **Studies III** and **IV**, we characterized the central representation of the space around the hand by using three-dimensional visual stimuli moving either close to or far from the participants' right hand. The participants maintained their gaze on a fixation point but had a direct view of both their hand and the visual stimuli. This setup was used successfully in a recently published study where we found evidence for the existence of a shared representation of the space around one's hand and another person's hand (Brozzoli et al., 2013).

Improving the ecological validity of the setups also contributed to reducing the gap between the experiments presented here and the neurophysiological investigations on primates on which our neuroanatomical and functional hypotheses were predicated. Although air puffs and visual stimuli presented on computer screens have been used successfully with non-human primates (Duhamel et al., 1998; Cooke and Graziano, 2003; Avillac et al., 2007), numerous studies have capitalized on the efficacy of naturalistic, three-dimensional visual and/or tactile stimuli presented in direct view of the animals (Rizzolatti et al., 1981a, 1981b; Graziano and Gross, 1998; Graziano, 1999; Graziano et al., 2000). These observations contributed to the selection of the sensory stimuli in our neuroimaging experiments.

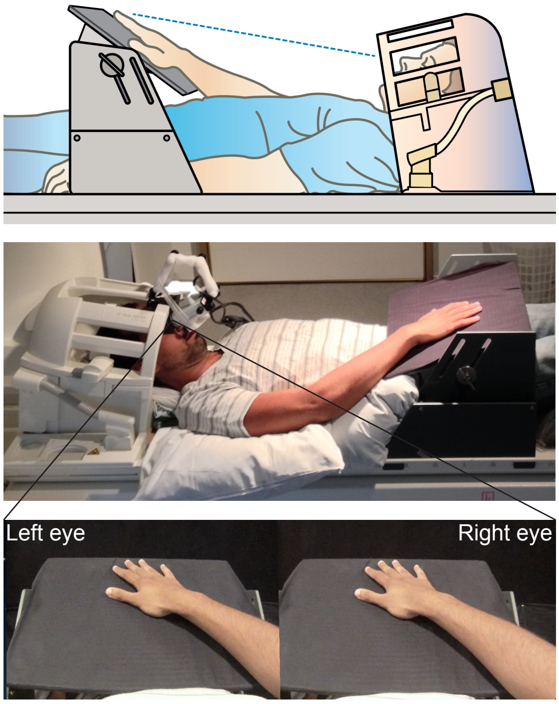

Figure 5. Top panel: in Studies I, III, and IV, we employed an ecologically valid setup where the participants had their head tilted forward to allow them to look directly at their right hand, placed on a tilted support above their waist, and at the visual and tactile stimuli (sketch adapted from Brozzoli et al., 2013). Middle panel: in Studies II and V, we developed a setup based on virtual reality technology to manipulate the self-attribution of the participants' right hand. Bottom panel: three-dimensional videos were presented to the participants through MRI-compatible head-mounted displays.

As part of the effort to improve the ecological validity of the setups, the visuo-tactile stimuli to the participants' hand were delivered *manually* using three-dimensional objects. This required that supplementary cautionary procedures be taken to ensure that the aggregate amount and the relative timing of the stimuli would be well controlled and consistent across the experimental conditions and the participants. In all the studies, the experimenters followed appropriate metronomes to time the presentation of the visual and/or tactile stimuli. In pilot experiments for **Study II**, as well as in all the acquisition sessions for **Study V**, the manually delivered tactile stimuli were tracked using an instrumented probe. In Study V, a force sensor was mounted on the three-dimensional object used to deliver the tactile stimuli. This allowed the registering of data concerning the timing, force, and duration of each tactile stimulus (see Figure 6 for an example). The pooled data from all the experiments revealed that the average timing error for the tactile stimuli, computed against the corresponding visual stimuli, was smaller than 100 milliseconds. Importantly, none of the participants reported any perceived delay between the visual and tactile stimuli when the latter two were supposed to be synchronous. This is consistent with previous studies that have shown that the perceptual binding of visual and tactile signals from the hand is drastically reduced if a delay larger than roughly 200-300 milliseconds is introduced between the two sensory streams (Shimada et al., 2005, 2009). Additional analyses revealed that the average time error, as well as the duration and force associated with each manually delivered stimulus, did not differ significantly between the experimental conditions. The above remarks clarify that the choice to have the stimuli delivered manually by the experimenters, contributing to the ecological validity of the setups, did not compromise the accuracy of the presentation of the stimuli and did not introduce any significant difference between the experimental conditions that may have confounded the analyses.

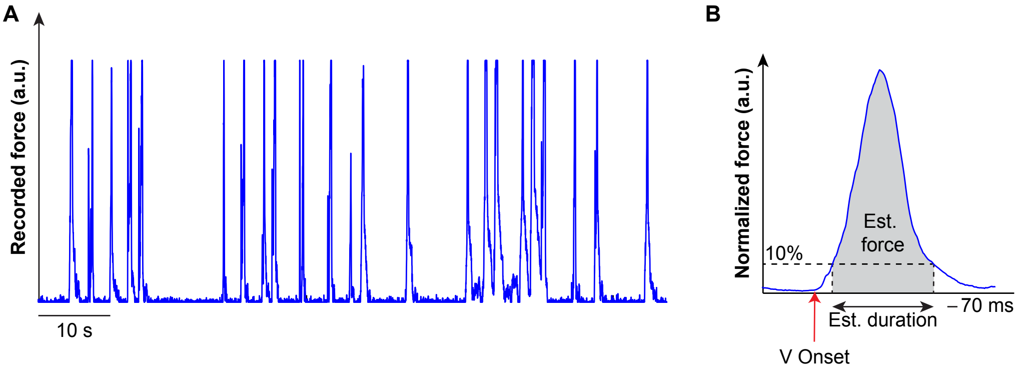

Figure 6. (**A**) Example or the raw, unfiltered data recorded with an MRI-compatible force sensor in Study V (see the corresponding manuscript for details). The time course corresponds to the force recorded as a function of time while the tactile stimuli were delivered manually by the experimenter to the participants' right hand in the scanner. (**B**) Example of the quantitative information extracted from the representative time course for a tactile stimulus.

In light of all the above considerations, we set out to design fMRI experiments with the goal of maximizing the ecological validity of the setups without forfeiting the high sensitivity in detecting BOLD responses to naturalistic sensory stimuli delivered to the participants' hand. We propose that the methodological features summarized above constitute a straightforward yet significant advancement compared to previous studies. Furthermore, they help reduce the gap between the rich body of neurophysiological research in non-human primates and the more recent neuroimaging studies in humans that were reviewed in the Introduction.

4.10 A VIRTUAL REALITY SETUP TO INVESTIGATE THE SELF-ATTRIBUTION OF THE HAND

In order to extend the investigation of the mechanisms underlying multisensory integration and the representation of the peripersonal space to encompass the psychological and neural phenomena associated with the self-attribution of the hand, we developed a setup based on virtual reality techniques that allowed the use of more complex experimental conditions. Despite the advantages associated with the simple, ecologically valid setups described above, the specific experimental manipulations in **Studies II** and **V** required the introduction of an appropriate virtual reality platform. Explicitly, the manipulation of the spatio-temporal congruence of the multisensory signals from the upper limb, as well as the introduction of unexpected sensory omissions that was crucial to the design of Study V, would not have been possible with the experimental setups we adopted in Studies I, III, and IV.

In order to overcome these limitations, we set out to develop a platform based on virtual reality tools that would deviate as little as possible from the ecologically valid setups described above. Specifically, we chose to adopt pre-recorded visual stimuli that featured the participants' own right hand, a step that allowed us to gain insights on the link between multisensory integrative mechanisms and the self-attribution of one's own hand, as opposed to an artificial body part or object (Botvinick, 2004; Moseley, 2011; Ehrsson, 2012). The visual stimuli were custom-made and consisted of high-quality stereoscopic videos that were presented to the participants in the MRI scanner via a pair of head-mounted displays placed right next to their eyes (Nordic Neuro Lab, Bergen, Norway; see also Petkova et al., 2011). All the other aspects of the experimental setups for **Studies II** and **V** were kept as similar as possible to the other studies. Namely, the participants had their head tilted forward and their right hand placed on the same inclined support, while looking at the three-dimensional videos through the head-mounted displays (Figure 5). Furthermore, the tactile stimuli associated with the videos were delivered manually by the experimenter following the same procedures described in the other studies. Special care was taken to ensure that the position of the participants' hand in the scanner matched as closely as possible the position of the hand in the videos. As mentioned previously, this arrangement allowed us to introduce a number of experimental manipulations that would not have been feasible without the virtual reality platform.

In **Study II**, we significantly disrupted the perceptual binding of visual, tactile, and proprioceptive signals from the upper limb by introducing highly noticeable temporal delays, spatial incongruences, or mismatches between the seen and felt postures of the hand. Thus, we were able to relate the degree of the neural integration of the multisensory signals to the strength of the self-attribution of the hand, as indexed by subjective measures of visuo-tactile-proprioceptive perceptual binding and the sense of limb ownership. Furthermore, the use of pre-recorded videos permitted the introduction of effective threat stimuli (a kitchen knife sliding just above the pre-recorded video image of the hand), which allowed the recording of threat-evoked psychophysiological and neural responses. The latter measures served as complementary evidence for changes in the self-attribution of the hand as a function of the congruence between the multisensory signals. All the participants reported a vivid feeling of ownership toward the video image of their right hand only in the presence of congruence between visual, tactile, and proprioceptive signals. The participants' subjective reports, corroborated by the complementary objective measures, confirmed the effectiveness of the experimental manipulations, particularly with respect to the marked reduction in the perceptual binding induced by the incongruences between the sensory signals in the control conditions. Taken together, these observations validated the virtual reality setup as a tool to induce changes in the self-attribution of the hand as a function of the congruence between the sensory signals from the upper limb.

The virtual reality setup was perhaps even more crucial to the design of **Study V**. In that study, we combined the manipulation of the multisensory congruence of signals from the hand employed in Study II with the introduction of unexpected omission trials. In the latter, one of the components of a multisensory event was unpredictably omitted, with the goal of unveiling the existence of multisensory predictions concerning self-attributed stimuli. The unpredictable omission of a visual or tactile stimulus, while maintaining the non-omitted stimulus intact, would have proven to be a severe methodological challenge without the use of the virtual reality setup. With the use of the latter, we were instead able to (1) change the self-attribution of the hand as a function of the congruence between the signals, and (2) introduce unexpected sensory omission events in multiple sensory modalities. In summary, we developed a setup based on virtual reality tools for use in fMRI studies that significantly extended the potential of introducing more sophisticated experimental manipulations to investigate how the integration of signals from multiple sensory modalities relates to the representation and self-attribution of one’s hand.

4.11 MONITORING THE PARTICIPANTS’ ALERTNESS: CATCH TRIALS AND EYE MOVEMENTS

In order to ensure that participants remained as alert as possible during the fMRI acquisition sessions, we used a combination of simple catch trials and eye-tracking methods. The catch trials were designed to be fully orthogonal to the experimental manipulations of interest, and required a button press with the left hand whenever the target stimulus occurred. For instance, in **Studies III** and **IV**, the catch trials consisted of replacing the moving visual stimulus (the three-dimensional objects moving close to or far from the participants’ right hand) with a static stimulus (non-moving object). The catch trials were uniformly distributed among the experimental conditions, and did not require the participants to assess the relative position of the visual stimulus with respect to the position of their right hand. In **Studies II** and **V**, the catch trials consisted of replacing the moving visual or tactile stimuli with corresponding static stimuli, or briefly changing the color of the visual stimulus (the object touching the hand). Again, the distribution of the catch trials was identical for all conditions and was fully orthogonal to the manipulation of the self-attribution of the participants’ right hand. All of the participants performed with high accuracy with respect to the catch trials, which were included in the general linear model as regressors of no interest.

To further monitor the participants’ alertness throughout the experimental sessions, we employed an MRI-compatible video camera (acquisition frequency 60 Hz; MRC Systems, Heidelberg, Germany) to track movements of the left eye. In **Studies II** and **V**, the camera was mounted next to the left head-mounted display (see Figure 7 for an example), whereas in **Studies III** and **IV** the camera was mounted on the head coil and placed next to the participants’ left eye. The recordings were monitored online by an experimenter in the MRI control room, and examined offline to evaluate the participants’ overall alertness. Furthermore, the monitoring of the participant’s left eye allowed us to rule out the possibility that systematic differences in condition-specific patterns of eye movements would contribute to the BOLD responses in the vicinity of the brain regions of interest. Abundant evidence – ranging from electrophysiological studies in non-human primates to human neuroimaging studies – supports the existence of neuronal populations in the frontal and parietal lobes that are specialized in the planning, performance, and control of eye movements. Two regions, the frontal eye fields and the intraparietal sulcus, are key nodes in the brain circuits devoted to the control and execution of eye movements, with an emphasis on object-directed eye movements that help guide the use of the hands to interact with objects (Johansson et al., 2001; Flanagan and Johansson, 2003; Grefkes and Fink, 2005; Culham et al., 2006; Andersen and Cui, 2009).

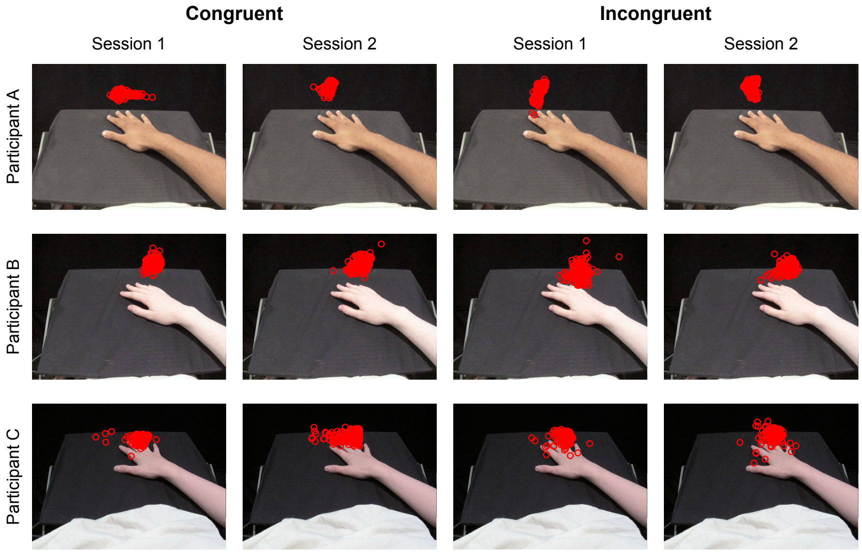

Figure 7. Examples of the eye-tracking data acquired to monitor the participants' alertness. The data display the raw data from all scanning sessions for three representative participants in Study V. The participants were instructed to maintain their gaze around the location of the hand and the visual stimulus that appeared just above the hand and came in contact with it. Each red circle represents the x and y position of the participant's left pupil averaged over a period of 500 ms (the data were sampled at 60 Hz) and overlaid onto the left frame of the videos presented to the participants.

In light of the above, two main reasons emerge to support the use of basic eye monitoring techniques in the experiments described in the thesis. First, we were able to ensure that the BOLD responses we consistently observed in regions of the frontal and posterior parietal lobes would not be confounded by systematically different patterns of eye movements between the experimental conditions. Second, with particular relevance to **Studies III** and **IV**, we were able to characterize the hand-centered properties of the neural representation of the perihand space by ensuring that the relative position of a visual stimulus would vary only with respect to the location of the participants' hand and not with respect to their eyes, which they were required to maintain on a central fixation point. In summary, through a combination of simple catch trials and eye monitoring techniques, we were able to assess the participants' overall alertness during the fMRI acquisition sessions. Importantly, the monitoring of the participants' eye movements also contributed to strengthening all the conclusions drawn from the neuroimaging experiments, with a prominent role in the studies that characterized the hand-centered representation of the space around the upper limb.

4.12 POST-SCAN EXPERIMENTS: CONNECTING BEHAVIORAL AND BOLD MEASURES

A considerable advantage associated with performing neuroimaging experiments with human volunteers is the unique opportunity to link psychophysiological and neural responses to the subjective experience of complex psychological phenomena. This benefit stands out against similar experiments performed on other animals and non-human primates that, despite the potential for greatly enhanced spatio-temporal resolution, fall short of capitalizing on the exquisitely human ability to report on complex behavioral experiences using language and other implicit or explicit channels. These general considerations apply especially well to the investigation of the psychological and neural mechanisms underlying the sense of ownership experienced over one's body parts. Starting with the seminal report by Botvinick and Cohen (Botvinick and Cohen, 1998), a plethora of studies have capitalized on the accessibility to the subjective experience of body ownership granted by human research volunteers (Costantini and Haggard, 2007; Ehrsson, 2007; Lenggenhager et al., 2007; Petkova and Ehrsson, 2008; Slater et al., 2008; Barnsley et al., 2011; Tsakiris et al., 2011). More recently, neuroimaging investigations of bodily self-perception have consistently demonstrated a tight link between the BOLD responses to multisensory stimuli and the strength of the subjective experience of ownership of a limb or a whole body (Ehrsson et al., 2004; Ionta et al., 2011b; Petkova et al., 2011a; Guterstam et al., 2013).

In light of the above, we employed an array of behavioral measurements to assess the participants' subjective experience of the experimental conditions of interest, with a focus on the self-attribution of the upper limb. In **Studies II**, **IV**, and **V**, the participants were presented with additional repetitions of the experimental conditions following the completion of the fMRI acquisition sessions. Immediately after each repetition, the participants were asked to rate a number of statements that were aimed at probing their subjective experience associated with the experimental conditions. Several statements targeted the subjective experience of ownership of the hand (a three-dimensional video image of the participants' right hand in Studies II and V, and a prosthetic hand in Study IV), and were adapted from previous behavioral and neuroimaging studies (Botvinick and Cohen, 1998; Ehrsson et al., 2004; Tsakiris et al., 2007; Dieguez et al., 2009). The remaining statements served as control for the potential effects of task demands and suggestibility. The subjective ratings were collected via verbal reports and logged for offline analysis. Through unbiased multiple regression analyses, we were able to test for potential relations between the BOLD responses to the experimental conditions of interest and the subjective reports. Such analyses offer a powerful tool to capture inter-individual variability in both brain responses and subjective experiences, constructing a straightforward albeit indirect model describing the link between the neural and behavioral correlates of the self-attribution of the upper limb. One possible caveat, pertaining to the interpretation of the findings from post-scan behavioral experiments, deserves further comments. In all the post-scan behavioral tests, the subjective rating to the various experimental conditions were collected only once per participant. As such, they are interpreted to reflect the participants' overall subjective experience of each experimental condition, failing to capture the trial-by-trial variability that could be associated with the high number of repetitions typically included in neuroimaging experiments. Notwithstanding this limitation, the post-scan behavioral experiments cash in on the existing inter-individual differences and provide sufficient statistical power to detect robust correlations between the neural and behavioral measures of the sense of ownership of the hand (Ehrsson et al., 2004, 2005, 2007; Tsakiris et al., 2007; Petkova et al., 2011a; Guterstam et al., 2013).

In **Study IV**, the post-scan behavioral experiments included an additional test to quantify the changes in the perceived location of one's own hand. Following periods of congruent visuo-tactile stimulation, the participants began to refer somatic sensations and the subjective feeling of ownership to a prosthetic hand placed close to their hidden right hand (the *rubber hand illusion*; Botvinick and Cohen, 1998). These changes in the self-attribution of the prosthetic hand are often accompanied by a recalibration of the perceived location of the hand toward the prosthetic hand, termed *proprioceptive drift*, that typically ranges between 10 and 20% of the total distance between the veridical and artificial hands (Botvinick and Cohen, 1998; Tsakiris et al., 2007; Guterstam et al., 2011; Kalckert and Ehrsson, 2012). The proprioceptive drift, measured by simple inter-manual pointing tasks, is interpreted within the framework of existing models of bodily self-perception as reflecting the recalibration of the perceived location of the hand that accompanies the integration of congruent visual signals from the prosthetic hand and tactile signals from the real hand (Makin et al., 2008; Tsakiris, 2010; Blanke, 2012; Ehrsson, 2012). However, a number of recent studies have put into questions the assumption that the proprioceptive drift and the subjective sense of ownership are two manifestations of the same neuronal mechanisms (Holmes et al., 2006; Folegatti et al., 2009; Rohde et al., 2011). The proprioceptive drift, considered to rely primarily on visuo-proprioceptive integration, resembles the changes in the perceived location of the hand that arise from a resolvable conflict between visual and proprioceptive signals, as is the case with prism adaptation (Redding et al., 2005; Folegatti et al., 2009; Newport and Schenk, 2012) or mirrors (Holmes and Spence, 2005b; Holmes et al., 2006; Snijders et al., 2007). In the above examples, the recalibration of hand position is not accompanied by changes in the self-attribution of the hand. Therefore, caution should be exercised when making inferences on the self-attribution of the hand based on data obtained exclusively from proprioceptive drift measurements (Folegatti et al., 2009; Rohde et al., 2011). Conversely, the co-assessment of the subjective sense of ownership and the proprioceptive drift opens a window for the investigation of two potentially separate neural mechanisms that can be turned into an advantage by appropriately designing the experimental paradigms. With this in mind, we devised the post-scan behavioral experiments in **Study IV** to include measurements of both the subjective feeling of ownership and the proprioceptive drift. While the former were used to quantify changes in the self-attribution of the prosthetic hand, the latter were employed only to assess the recalibration of the perceived hand position. We then exploited the likely dissociation between the two types of measures to test for differences in their relation to the spatial remapping of the representation of the space around the hand.

In summary, we took advantage of the above considerations, extracted from a rich body of literature, to maximize the gains specific to neuroimaging studies featuring human volunteers by collecting a variety of subjective indices quantifying the self-perception of the hand that we could relate to the corresponding BOLD responses. We extended this line of reasoning further to encompass additional measurements that would enrich the description of the multifaceted phenomena associated with the self-perception of one’s own body.

4.13 RECORDING AND ANALYSIS OF SKIN CONDUCTANCE RESPONSES DURING FMRI

The skin conductance response (SCR), also known as electrodermal activity or galvanic skin response, originates primarily from the increased activity of sweat glands regulated by the sympathetic nervous system in response to states of psychophysiological arousal (Malmivuo and Plonsey, 1995; Critchley, 2002). The SCR reflects small changes in the electrical conductance of the skin that can be measured by monitoring the flow of a steady current between two electrodes. The sensitivity of the SCR in detecting fluctuations in arousal induced by the presentation of emotional stimuli has contributed to its widespread use in psychology and cognitive neuroscience. With respect to investigating the perception of limbs and whole bodies as belonging to one's physical self, measuring the SCR to threats directed toward a body part serves as an objective measure of the sense of body ownership, preferably in complement to subjective (questionnaire ratings) and other objective (BOLD activity) indices, as described in the preceding section. Numerous studies have validated the use of the SCR to test the hypothesis that threats directed toward a self-attributed body part would lead to augmented psychophysiological arousal compared to the same threats directed toward body parts or objects that are not perceived as belonging to one's physical self (Armel and Ramachandran, 2003; Ehrsson, 2007; Ehrsson et al., 2008; Petkova and Ehrsson, 2008; Newport and Preston, 2010; van der Hoort et al., 2011; Guterstam et al., 2011, 2013; Newport and Gilpin, 2011; Tajadura-Jiménez et al., 2012; Farmer et al., 2012; Ferri et al., 2013a). To the best of our knowledge, no previous neuroimaging study on the sense of body ownership has recorded SCRs and linked them to the measured BOLD responses underlying the self-attribution of limbs or whole bodies.

In both **Study II** and **Study V**, we employed an MRI-compatible SCR recording device to register the participants' psychophysiological responses to threat events directed toward a virtual seen hand that was perceived either as belonging to one's physical self or not. In both studies, the pre-recorded threat stimulus consisted of a kitchen knife moving into the field of view of the head-mounted displays and sliding swiftly just above the virtual image of the participants' right hand. The duration of each threat stimulus was roughly 2 seconds. Similar threat stimuli have been used and validated in previous behavioral and neuroimaging investigations of the sense of body ownership (Lloyd et al., 2006; Ehrsson et al., 2007; Petkova and Ehrsson, 2008; Guterstam et al., 2013).

Given the technical constraints imposed by the strong magnetic field, special hardware is necessary to acquire high-quality SCR data during fMRI. Prior to the onset of the scanning sessions, two electrodes were attached to the index and middle fingers of the participants' left hand. Once the participants were positioned inside the MRI scanner, the electrodes were attached to an MRI-compatible signal amplifier (BrainAmp ExG MR, Brain Products, Gilching, Germany), placed next to the participants' body. The signal was then carried to the MRI control room via a fiber optics connection and sampled at a frequency of 5 kHz using a computer running the Brain Vision Recorder software (Brain Products). The recordings were synchronized with the acquisition of the fMRI data to ensure accurate timing information for offline analysis. The SCR data for each participant were loaded into Matlab and low-pass filtered (the cutoff frequency was set to 10 Hz) using the *eeglab* toolbox (Delorme and Makeig, 2004). In keeping with previous work (Dawson et al., 2007; Ehrsson, 2007; Petkova and Ehrsson, 2008; Guterstam and Ehrsson, 2012), the threat-evoked SCR data were analyzed as follows.

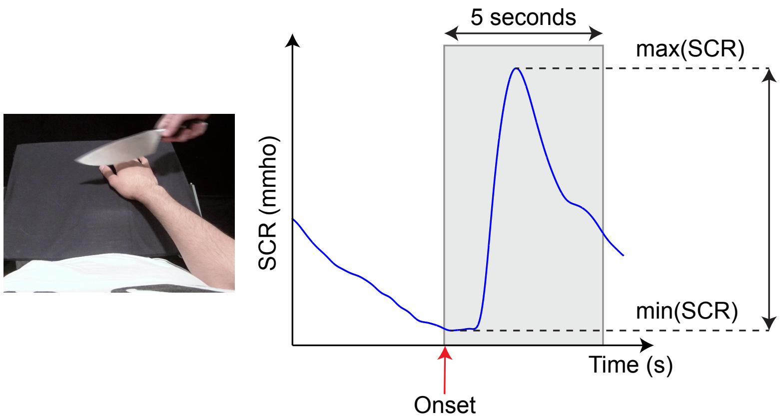

Figure 8. In Studies II and V, we recorded threat-evoked SCRs during fMRI as psychophysiological evidence for changes in the self-attribution of the hand. The SCR to each occurrence of the threat stimulus was analyzed by defining a 5-second window aligned to the event onset and subtracting the minimum value from the maximum value within that time window.

For each repetition, experimental condition, and participant, we extracted the signal corresponding to a 5-second time window aligned to the onset of the threat event. We then calculated the amplitude of the SCR as the difference between the maximal and minimal values identified within that time window (Figure 8). The average response was then computed for each condition and each participant, and the data were imported into SPSS (IBM Corporation, Armonk, NY, USA) for further statistical analysis. The SCR data from Study II passed the Kolmogorv-Smirnoff test for normality and were analyzed using a 2x2 repeated-measures analysis of variance (Interaction term: *Visuo-tactile congruence* x *Visuo-proprioceptive match*), whereas the data from Study V were not normally distributed and were analyzed using a non-parametric paired two-tailed Wilcoxon Signed Ranks test (*Congruent* vs. *Incongruent*).

Besides granting the opportunity to record SCR data as an objective evidence for the self-attribution of the hand, an additional advantage with the presentation of threat events to the participants during fMRI resides in the potential to measure the corresponding threat-evoked changes in the BOLD response. Several neuroimaging studies have demonstrated that the anticipation and the emotional response associated with nociceptive stimuli delivered to the hand induce reliable changes in the BOLD signal in regions of the anterior cingulate and insular cortices (Critchley et al., 2003; Singer et al., 2004; Wager et al., 2004; Farrell et al., 2005; Lloyd et al., 2006; Ehrsson, 2007). In light of this, in **Study II** we presented the changes in the BOLD response evoked by the threat stimuli, alongside the corresponding SCR data. Furthermore, we performed independent multiple regression analyses to relate the psychophysiological SCRs to the BOLD indices quantifying the integration of multisensory signals from the hand. Together with the subjective ratings obtained from the post-scan questionnaires, these psychophysiological (SCR) and neural (BOLD) objective measures contributed to shape the battery of complementary tests that we adopted to quantify the psychological phenomena associated with the self-attribution of the hand.

5 RESULTS AND SHORT DISCUSSION

The aim of this section is to recapitulate the main findings from the studies presented in the thesis, in conjunction with a short discussion of the strengths and weaknesses associated with their interpretation. For in-depth details, the reader is referred to the attached articles and manuscripts.

5.1 STUDY I: VISUO-TACTILE INTEGRATION IN CORTICAL AND SUBCORTICAL BRAIN REGIONS

The purpose of Study I was to identify cortical and subcortical brain regions that perform the integration of visual and tactile signals from one's own hand. In light of the abundant evidence from neurophysiological research in non-human primates (Graziano and Botvinick, 2002), as well as more recent neuropsychological and neuroimaging studies in humans (Driver and Noesselt, 2008; Heed and Röder, 2012; Murray and Wallace, 2012), we hypothesized the existence of multisensory neuronal populations in frontal, parietal, and subcortical human brain regions that are sensitive to both visual and tactile signals from the hand and display a response profile to congruent visuo-tactile stimuli compatible with multisensory integrative mechanisms. We employed an ecologically valid experimental setup whereby the participants received visual, tactile, and combined visuo-tactile stimuli while looking directly at their right hand during the fMRI acquisition sessions.

In an fMRI experiment with twenty-four healthy human volunteers, we compared the BOLD responses to unisensory visual and tactile stimuli with the responses to congruent visuo-tactile stimuli delivered to the participants' right hand (Figure 9A). A conjunction analysis of the BOLD responses to the unisensory signals revealed areas of significant overlap in the left posterior and inferior parietal cortices, encompassing the anterior intraparietal sulcus, close to the junction with the postcentral sulcus and the superior parietal gyrus, and, more inferiorly, the supramarginal gyrus and the parietal operculum. In the frontal lobe, significant overlap was found in the ventral and dorsal portions of the left premotor cortex. At a lower threshold, the same effect was identified in the right inferior parietal cortex, and, subcortically, in the left putamen and in Lobule VI of the right lateral cerebellum. Hence, these results characterized a set of brain regions where the BOLD responses to visual and tactile stimuli to one's own hand converge significantly within the same voxels. These initial findings fit well with the extensive body of neurophysiological evidence reviewed in the Introduction, and served as a starting point for the characterization of the multisensory BOLD responses.

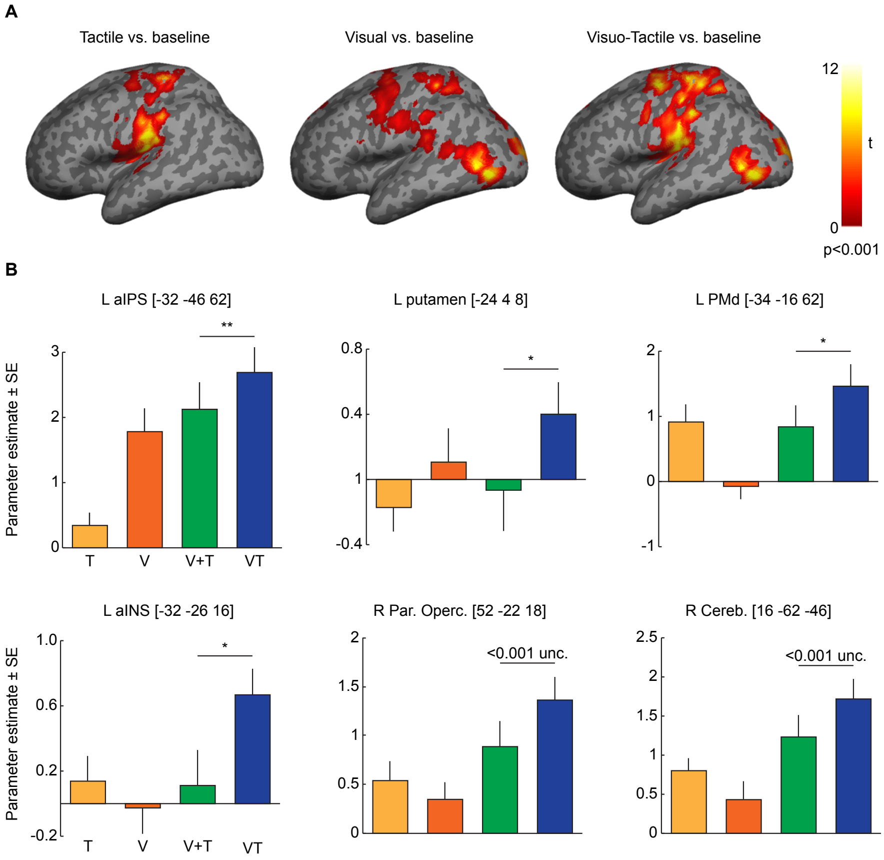

Figure 9. Summary of the main findings from Study I. (**A**). We compared the BOLD responses to ecologically valid tactile, visual, and congruent visuo-tactile stimuli delivered to the participants' right hand. The activation maps represent the responses to the unisensory and the multisensory conditions relative to a common baseline, thresholded at a p<0.001 and overlaid onto a representative inflated cortical surface of the left (contralateral) hemisphere. (**B**) Frontal, parietal, and cerebellar regions displayed non-linear superadditive BOLD responses to the visuo-tactile (VT) stimuli, i.e., responses that were significantly greater that the sum (V+T) of the BOLD responses to the unisensory tactile (T) and visual (V) conditions presented separately. Coordinates are given in MNI space. **p<0.01 corrected for multiple comparisons. *p<0.05 corrected.

In order to characterize the BOLD response profiles evoked by the combined visuo-tactile stimuli, we implemented a 2x2 factorial design controlling the presence or absence of the stimulation in either the visual or tactile modalities. The key findings emerged from the investigation of the positive interaction contrast obtained from the factorial design. With *R* being defined as the appropriate common baseline for all conditions, the factorial interaction contrast was expressed as $(VT\text{-}V) - (T\text{-}R) > 0$, where *VT* indicates the BOLD response to the congruent visuo-tactile stimuli, and *V* and *T* the unisensory BOLD responses to the visual and tactile stimuli, respectively. Simply rearranging the terms of the contrast yields the expression (*VT-R*) > (*V-R*) + (*T-R*), which clearly identifies it as a statistical test for superadditive *VT* responses. In other words, this contrast revealed voxels whose BOLD responses to the congruent visuo-tactile stimuli exhibited a superadditive profile that cannot be accounted for by non-interacting responses to the visual and tactile stimuli. Specifically, the superadditive responses necessarily reflect a non-linear interaction between the two sensory signals that is strongly indicative of multisensory integrative mechanisms. Superadditive responses to the visuo-tactile stimuli were found in the anterior segment of the left intraparietal sulcus, close to the junction with the postcentral sulcus, in the left posterior insula in the inferior parietal lobe, and in the left dorsal section of the premotor cortex in the frontal lobe (Figure 9B). At a lower threshold, superadditive responses were found in regions of the right inferior parietal cortex. Subcortically, the same response profile was identified in the left putamen, and, at a lower threshold, in the right cerebellum. Despite the caveats associated with the interpretation of the superadditive responses (see discussion in Methodological considerations), these results, obtained from a simple, ecologically valid set of experiments, demonstrate high neuroanatomical specificity and fit well with the a priori hypotheses. These findings identify fronto-parietal-subcortical brain areas that are likely to host the multisensory mechanisms underpinning the integration of visual and tactile signals from the hand.

To complement the results from the interaction contrast, we examined the two main effects derived from the factorial design. The conjunction of the main effects of visual and tactile stimulation revealed voxels whose BOLD response profile to the combined visuo-tactile stimuli is additive with respect to the responses to the unisensory signals. Such additive responses to the visuo-tactile stimuli were found in regions of the left posterior parietal cortex, encompassing the superior parietal gyrus, the postcentral sulcus, the supramarginal gyrus, and the parietal operculum. In the right parietal lobe, similar responses were found in the vicinity of the parietal operculum and the supramarginal gyrus. In the frontal lobe, the additive responses were found in the ventral and dorsal portions of the left premotor cortex. Subcortically, the same response profile was identified in the left ventrolateral thalamus and in Lobules VIIIa and VIIIb of the right cerebellum. Importantly, the examination of the main analyses in individual participants revealed that the findings were highly reproducible and consistent across individuals. Again, these results converge onto a set of parietal, frontal, and subcortical brain regions whose BOLD response profiles to the multisensory stimulation of the right hand suggest the existence of neuronal populations that integrate the signals from the upper limb across multiple sensory modalities.

The findings from Study I offer an important conclusion for the work presented in the thesis. The participants in this study were presented with visual, tactile, and visuo-tactile stimuli to their own right hand in direct view. Thus, the multisensory integration of visuo-tactile stimuli from one's own hand, in the absence of any recalibration of the position sense of the hand, illusory feelings of ownership toward artificial limbs, virtual reality tools, or task-related effects, results in the robust engagement of widespread frontal, parietal, and subcortical brain regions.

5.2 STUDY II: THE HAND'S SELF-ATTRIBUTION DEPENDS ON MULTISENSORY CONGRUENCE

The purpose of Study II was to describe the relation between the multisensory mechanisms underpinning the integration of visual, tactile, and proprioceptive signals from the upper limb and the self-attribution of the hand. To this aim, we developed a setup based on virtual reality techniques that allowed the introduction of experimental manipulations that would not have been possible with the setup used in Study I. During the fMRI acquisition sessions, the participants watched high-quality stereoscopic videos of their right hand being touched by a three-dimensional object, while receiving tactile stimulation on their right hand inside the MRI scanner. The virtual reality setup permitted the manipulation of the spatio-temporal congruence of the visual, tactile, and proprioceptive stimuli. By matching the visuo-tactile stimuli in time and space (or by introducing noticeable temporal delays or spatial incongruences), we were able to induce strong (or significantly break down) perceptual binding of the sensory signals from the hand. Furthermore, the participants' right hand was positioned in one of two different postures in the MRI scanner, allowing us to test for a three-way interaction between congruent visual, tactile, and proprioceptive signals from the upper limb. We hypothesized that the multisensory areas in the frontal, parietal, and subcortical regions identified in Study I would be sensitive to the congruence of the visual, tactile, and proprioceptive inputs. Furthermore, we predicted that the self-attribution of the hand would depend on the congruence of the inputs, with vivid self-attribution present only under conditions of congruence between the sensory inputs from the upper limb.

In two fMRI experiments on a total of thirty healthy human volunteers, we found that regions in the bilateral posterior parietal cortices, encompassing peaks located in the anterior segments of the intraparietal sulci and in the supramarginal gyri, were sensitive to the three-way congruence of visual, tactile, and proprioceptive signals from the hand. This ensued from a significant interaction in a 2x2 factorial design where we manipulated the congruence of visual and tactile signals from the hand, in conjunction with the match between visual and proprioceptive signals concerning hand position.

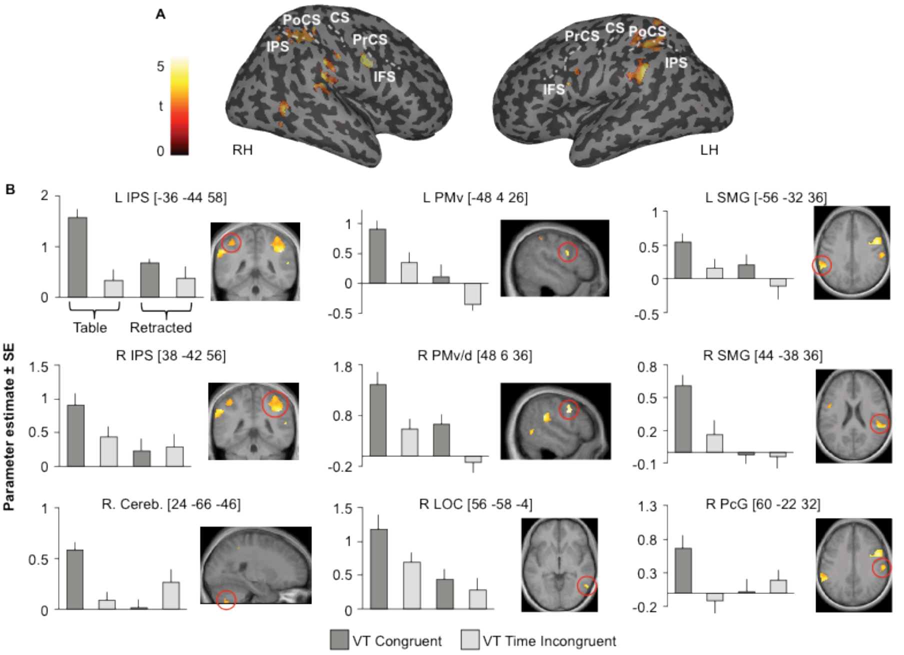

Figure 10. Overview of the main findings from Study II. (**A**) The manipulation of the congruence of the sensory signals from the hand revealed a three-way interaction between congruent visual, tactile, and proprioceptive signals in frontal, parietal, and cerebellar regions consistent with the findings from Study I. The corresponding activation map, thresholded at p<0.001 uncorrected for display purposes, is shown overlaid onto the representative inflated cortical surfaces of the left (LH) and right (RH) hemispheres. (**B**) Significant (all p<0.05 corrected) interactions between congruent visuo-tactile signals in the context of matching visuo-proprioceptive signals concerning hand position.

A similar response profile was found in portions of the bilateral ventral and dorsal premotor cortices in the frontal lobe, and, subcortically, in the right lateral cerebellum (Figure 10). A significant modulation of the BOLD response evoked by congruent multisensory signals from the hand was also observed in portions of the bilateral lateral occipito-temporal cortices. Furthermore, independent psychophysiological interaction analyses revealed that the effective connectivity between a seed region in the left anterior intraparietal cortex and the brain regions listed above varied as a function of the congruence between the multisensory signals from the hand, indicating that these areas work in concert to process the multisensory information from the hand. Finally, a separate control experiment revealed that the basic multisensory integrative effects are dissociated from the effects related to endogenous attention. Taken together, the main results summarized above, further replicated in Study V (see below for details), extend the findings from Study I and characterize a set of interconnected multisensory areas that integrate spatio-temporally congruent sensory stimuli from the upper limb.

The overarching aim of Study II was to relate the multisensory integration of visual, tactile and proprioceptive signals from the hand to the self-perception of the hand. As mentioned previously, the use of the virtual reality setup allowed us to manipulate the relative multisensory congruence of the signals from the participants' right hand and examine the ensuing neuronal and perceptual correlates.

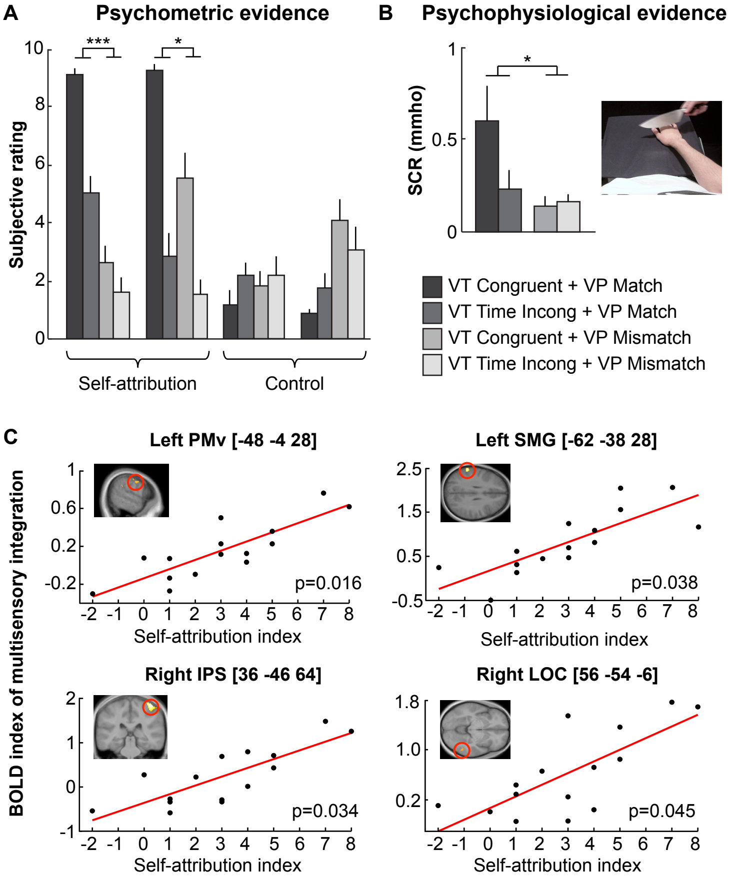

Figure 11. The self-attribution of the hand depends on multisensory congruence. (**A**) The post-scan experiments revealed that the participants experienced vivid self-attribution of the hand seen through the head-mounted displays only in the context of congruence between vision, touch, and proprioception. ***p<0.001, *p<0.05. (**B**) The threat-evoked SCRs revealed a significant interaction between visuo-tactile and visuo-proprioceptive congruence, displaying an enhanced psychophysiological response to the threat directed toward the hand when the latter was perceived as belonging to one's physical self. (**C**) The self-attribution index obtained from the subjective ratings significantly predicted the BOLD index of multisensory integration in key multisensory frontal and parietal regions.

We collected a battery of complementary subjective, psychophysiological, and neural measurements to link the multisensory integrative mechanisms to changes in the self-attribution of the hand seen through the head-mounted displays. Crucially, the post-scan behavioral experiments revealed that the participants experienced a strong feeling of ownership over the virtual image of their right hand only under conditions of congruence between the visual, tactile, and proprioceptive signals (Figure 11A). In other words, breaking down the congruence between the multisensory signals led to a feeling of disownership of the seen hand. The strength of the subjectively rated self-attribution of the hand correlated positively with the BOLD index of multisensory integration in key frontal and parietal areas, linking the neuronal processing in these regions to the experience of the seen hand as part of one's physical self (Figure 11C).

A direct prediction of the observed changes in the self-attribution of the hand relates to differences in the response to threat stimuli directed toward the virtual image of the hand. To test this hypothesis, we recorded the psychophysiological responses to threat stimuli directed toward the hand during the fMRI sessions and observed a significantly stronger threat-evoked skin conductance response in the context of the self-attribution of the hand, compared to the contexts characterized by the incongruent multisensory stimulation (Figure 11B). The magnitude of the threat-evoked psychophysiological responses scaled significantly with the BOLD measures of multisensory integration in key frontal and parietal areas, relating basic multisensory processing to the self-attribution of the hand. Furthermore, the BOLD responses to the threat-events indicated a differential engagement of areas related to the anticipation of noxious stimuli directed toward the hand (including the anterior cingulate and insular cortices; Ehrsson et al., 2007) and to the triggering of defensive movements aimed at protecting the body from incoming threats (including the premotor cortex and the cerebellum). The level of the activation of these circuits was greater following the congruent multisensory stimulation, further confirming that the seen hand was perceived as one's own only in the context of congruence between the sensory signals. In conclusion, complementary BOLD, subjective, and psychophysiological measures converge to indicate that the experience of the seen hand as part of one's physical body is intimately linked to the dynamic integration of multisensory signals originating from the upper limb.

5.3 STUDY III: THE CENTRAL REPRESENTATION OF THE PERIHAND SPACE

The aim of Study III was to provide neuroimaging evidence for the existence of a selective representation of visual stimuli presented in the space near to, as opposed to far from, the right hand. With this in mind, we developed an ecologically valid fMRI-adaptation paradigm whereby three-dimensional objects were presented close to (≈2 cm), or far from (100 cm), the participants' right hand. The right hand, always in direct view, was placed in one of two different postures across the experimental sessions, allowing us to dissociate the hand-centered responses to the visual stimuli from other spatial reference frames whose coordinate systems for the encoding of visual stimuli are not centered on the upper limb. We predicted stronger BOLD-adaptation to the stimuli presented in a spatial location within, as opposed to outside, the visual receptive fields of the putative perihand neuronal populations (Figure 12A).

The key finding of Study III the identification of frontal, parietal, and subcortical brain regions exhibiting BOLD-adaptation selective to the presence of an object in the perihand space. This finding is compatible with the existence of neuronal populations with visual receptive fields limited to the perihand space, revealing a mechanism for the selective representation of visual stimuli close to the hand. Neuronal populations with such properties were discovered in both cortical and subcortical brain regions and exhibited statistically significant BOLD-adaptation to the visual stimuli presented within the perihand space (Figure 12B). In the parietal lobe, neuronal populations with perihand RFs were found in the anterior segments of the bilateral intraparietal sulci, close to the junction with the postcentral sulcus, and at a more inferior location, with peaks encompassing the supramarginal gyrus in the left hemisphere. In the frontal lobe, we found evidence that portions of the bilateral ventral and dorsal premotor cortices contain neuronal populations with perihand RFs. Subcortically, the same was found in lobule VI of the left lateral cerebellum and, at a lower statistical threshold, in the right putamen. The above findings were obtained through two separate BOLD-adaptation analyses that proved to be more sensitive than a conventional analysis.

The selectivity of the above responses to the visual stimuli in the space near the hand was corroborated through two important observations. First, no statistically significant hand-centered BOLD-adaptation ensued from the presentation of the visual stimuli outside the perihand space, at a distance of 100 cm from the participants' right hand. Second, the statistically significant BOLD-adaptation obtained when the hand was positioned in the vicinity of the object was abolished when the participants' right hand was retracted away from that same spatial location.

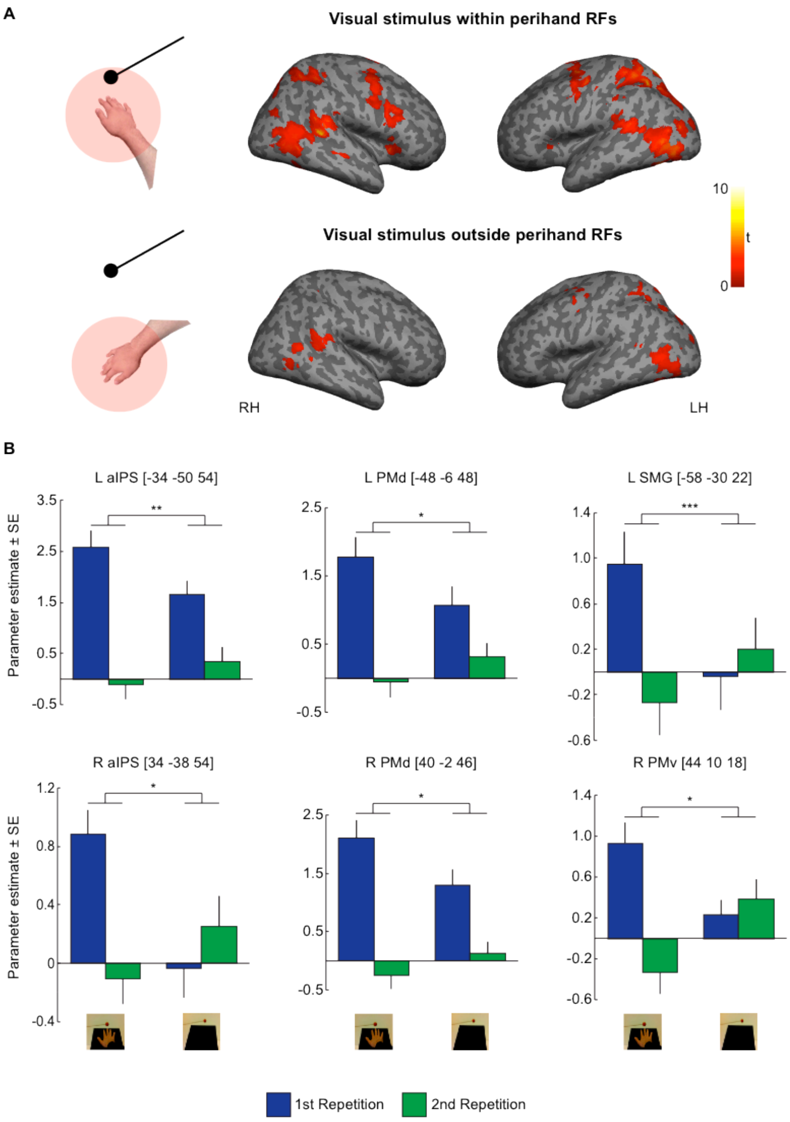

Figure 12. Overview of the main findings from Study III. (**A**) We found increased BOLD-adaptation to the presentation of a three-dimensional visual stimulus within, as opposed to outside, the perihand space representations. (**B**) We contrasted the BOLD responses to the first and second parts of the presentation of the visual stimulus both when the hand was present and when it was retracted. A significant interaction was found in regions of the frontal, parietal, and cerebellar cortices, revealing selective BOLD-adaptation to the presentation of the object within the visual receptive fields of perihand neuronal populations, in keeping with neurophysiological data from non-human primates.

Taken together, the above results advocate the existence of a set of frontal, parietal, and subcortical human brain regions that contain neuronal populations with visual RFs centered on the hand and restricted to the space immediately surrounding the upper limb. Furthermore, the neuroanatomical convergence between the set of brain regions identified in Studies I and II and the findings from Study III constitutes further support for the notion that the multisensory neuronal populations that integrate visual, tactile, and proprioceptive signals from the limb are equipped with visual receptive fields that are restricted to the immediate space around the hand.

5.4 STUDY IV: THE PERIHAND SPACE AND ITS LINK TO THE SELF-PERCEPTION OF HAND

The motivation behind Study IV was twofold. First, we sought to extend the findings of Study III and demonstrate that the selectivity for objects in the perihand space is anchored to the hand, i.e., the perihand space representation is remapped when the hand changes position in space. Second, we aimed at providing evidence for a connection between the perihand space representation and the feeling of ownership and the position sense of the hand.

In a first experiment on twenty-six healthy human volunteers, we adapted the BOLD-adaptation paradigm developed in Study III and characterized the hand-centered properties of the perihand space representation. A 2x2 factorial design was implemented, with factors related to the two spatial locations of the participants' right hand and of the three-dimensional object. In other words, this design manipulated the relative spatial proximity of the participants' right hand to the object, while controlling for all effects other than the presence of a visual stimulus in the visual RFs of the perihand neuronal populations (Figure 13A). The positive interaction contrast obtained from this design allowed us to identify brain regions exhibiting BOLD-adaptation responses selective to the presence of an object in the perihand space, regardless of the absolute spatial location of the upper limb. This finding would be compatible with the existence of neuronal populations that remap their visual RFs as the upper limb changes position in space, providing a selective mechanism for the encoding of visual stimuli in a hand-centered coordinate system.

In strong agreement with the findings from Study III, we found a significant interaction in the bilateral anterior and medial segments of the intraparietal sulci in the parietal lobes, and in ventral and dorsal portions of the bilateral premotor cortices in the frontal lobes (Figure 13C). At a lower threshold, the same was found in the right inferior parietal cortex and, subcortically, in the right putamen. Thanks to the nature of the factorial design, we were able to dissociate the hand-centered encoding of the visual stimulus from other spatial reference frames, such as the one defined in eye-centered retinotopic coordinates. These results extend the findings from the previous study and demonstrate that the perihand representation is updated dynamically when the upper limb moves in space, i.e., the perihand space representation is anchored to the hand.

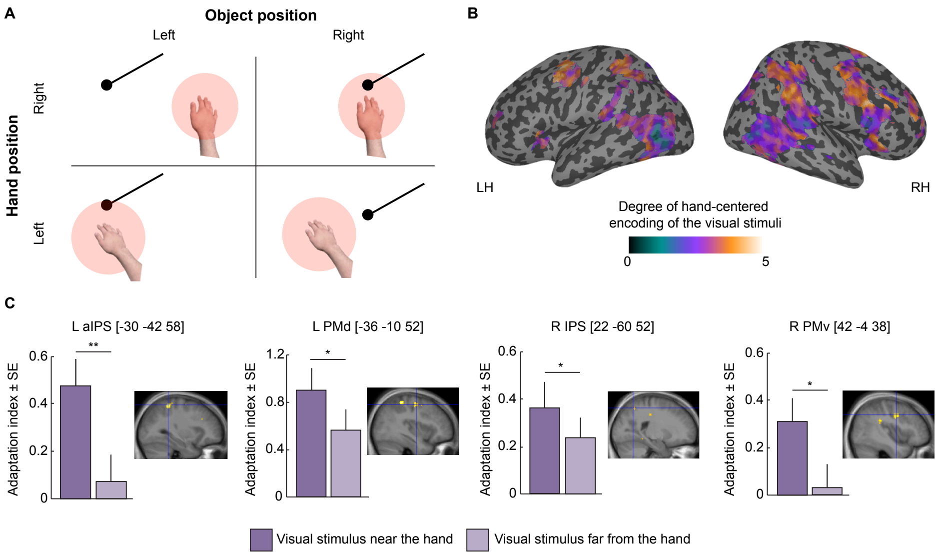

Figure 13. Overview of the main findings the first experiment in Study IV. (**A**) We employed a 2x2 factorial design where we manipulated the spatial locations of a three-dimensional visual stimulus and of the participants' right hand. (**B**) We found a marked gradient of hand-centered encoding of the visual stimulus in frontal and parietal areas identified in Study III. (**C**) The interaction contrast from the factorial design revealed voxels showing enhanced BOLD-adaptation for the presence of a visual stimulus within the visual RFs of the perihand neuronal populations, independently of the spatial location of the hand. This effect was found in regions of the posterior parietal and frontal cortices, including the intraparietal sulcus and the premotor cortex. $^{**}p<0.01$ corrected for multiple comparisons. $^{*}p<0.05$ corrected.

In a second fMRI experiment on sixteen healthy human volunteers, we tested the hypothesis that the central representation of the perihand space would be related to the feeling of ownership and the sense of position of the hand. To this aim, we employed the rubber hand illusion paradigm (Botvinick and Cohen, 1998; Ehrsson et al., 2004) to experimentally manipulate both the self-attribution of a prosthetic hand (the subjective sense of ownership) and the perceived spatial location of the hand (the position sense of the hand). In the post-scan experiments, the participants reported a significantly stronger feeling of ownership over the artificial hand when exposed to congruent, as opposed to incongruent, visual and tactile stimuli delivered to the artificial and veridical hands, respectively (Figure 14A). An inter-manual pointing task employed to assess the perceived location of the hand revealed a significantly larger drift toward the prosthetic hand in the illusion condition as opposed to the control condition (Figure 14B). The subjective and objective measures of the vividness of the rubber hand illusion were accompanied by an increase in the BOLD-response to the temporally congruent, as opposed to incongruent, visuo-tactile stimuli (Figure 14C). This was found in the anterior segment of the right intraparietal sulcus, in the bilateral inferior parietal lobes (with peaks centered on the supramarginal gyri), and in the bilateral ventral premotor cortices. The above results confirmed that the participants experienced a stronger sense of limb ownership following periods of congruent visuo-tactile stimulation.

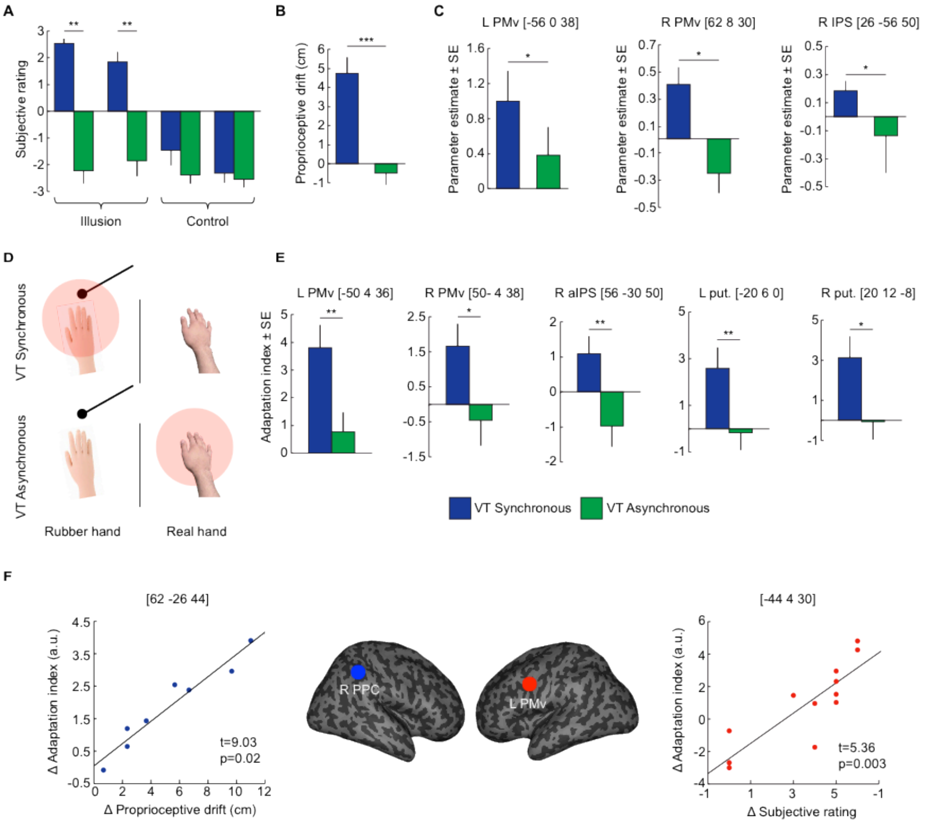

Figure 14. Overview of the main findings from the second fMRI experiment in Study IV. (A) The post-scan behavioral experiments confirmed that the participants experienced the artificial hand as belonging to their body more vividly following the synchronous, as opposed to the asynchronous, visuo-tactile stimuli. **p<0.01. (**B**) Following the induction of the illusion, the participants remapped the perceived location of their right hand towards the position of the artificial hand, as shown by a larger proprioceptive drift in the synchronous, as opposed to the asynchronous, condition. ***p<0.001. (**C**) Activity in multisensory regions of the posterior parietal and premotor cortices was greater for the synchronous, as opposed to the asynchronous, visuo-tactile stimuli, providing neural evidence for the embodiment of the artificial limb. *p<0.05 corrected for multiple comparisons. (**D**) The embodiment of the artificial hand was associated with a remapping of the perihand visual RFs to encompass its surrounding space. (**E**) Significant effects were found in the frontal and parietal areas identified before, as well as, subcortically, in the putamina. (**F**) The perihand spatial remapping in the posterior parietal cortex was related to the proprioceptive drift toward the artificial hand when the latter was embodied, whereas the subjective feeling of ownership correlated with the perihand spatial remapping in the ventral premotor cortex.

The BOLD-adaptation paradigm used in the first experiment was then employed to test the extent of the remapping of the perihand space representation to incorporate the artificial hand. Importantly, we found that a visual stimulus appearing and moving close to the artificial hand was encoded as within perihand space only when the hand was experienced as belonging to one's physical self (Figure 14D). In other words, we found significantly stronger BOLD-adaptation to the visual stimulus presented close to the artificial hand following the congruent, as opposed to the incongruent, visuo-tactile stimulation. This effect was identified in the anterior segment of the right intraparietal sulcus, in the bilateral ventral premotor cortices, and, subcortically, in the bilateral putamina (Figure 14E). At a lower threshold, the same response profile was found in the left anterior intraparietal sulcus, and in portions of the bilateral inferior parietal cortices. These results establish that the remapping of the perihand space representation occurs in conjunction with the dynamic changes in the self-attribution and localization of the hand in space. As such, they provide the first neuroimaging evidence linking the representation of the perihand space to the feeling of ownership and the sense of position of the hand. This observation represents an important conclusion towards the aims that motivated the work presented in this thesis.

We further corroborated the above observations by directly relating the extent of the spatial remapping of the perihand space, as indexed by the BOLD-adaptation measures, to the subjective and objective indices of the self-perception of the hand obtained in the post-scan experiments. Independent and anatomically unbiased multiple regression analyses revealed two main findings. First, we found a significant positive correlation between the strength of the subjective feeling of ownership over the artificial hand and the BOLD-adaptation index in the ventral premotor cortex that assesses the remapping of the perihand space representation toward the artificial hand (Figure 14F). Second, we observed a significant positive correlation between the relative proprioceptive drift toward the artificial hand and the same BOLD-adaptation index in a region of the right posterior parietal cortex, centered on the supramarginal gyrus. These results suggest a potential dissociation between the parietal mechanisms, underpinning the multisensory spatial localization of the upper limb, and the premotor mechanisms, reflecting the subjective feeling of ownership of the hand.

In a separate fMRI control experiment on nine volunteers, we reproduced the above findings in a paradigm where we varied the distance between the visual stimulus and the artificial hand. The participants always received synchronous visuo-tactile stimuli to the real and artificial hand, which led to the illusory embodiment of the latter, as confirmed by the same type of subjective (questionnaires) and objective (proprioceptive drift) data collected in the main experiment. Following the induction of the ownership illusion, the three-dimensional object was presented either close to the embodied rubber hand, as in the previous experiment, or 100 cm away from it, the same control distance used in the design of Study II (Figure 15). The comparison of the BOLD-adaptation effects following the presentation of the objects at the two spatial locations relative to the artificial hand revealed greater adaptation in the key areas identified in the main experiments, including the anterior and medial segments of the bilateral intraparietal sulci and portions of the bilateral ventral premotor cortices (unpublished data from a fixed effects model on nine participants; Figure 15).

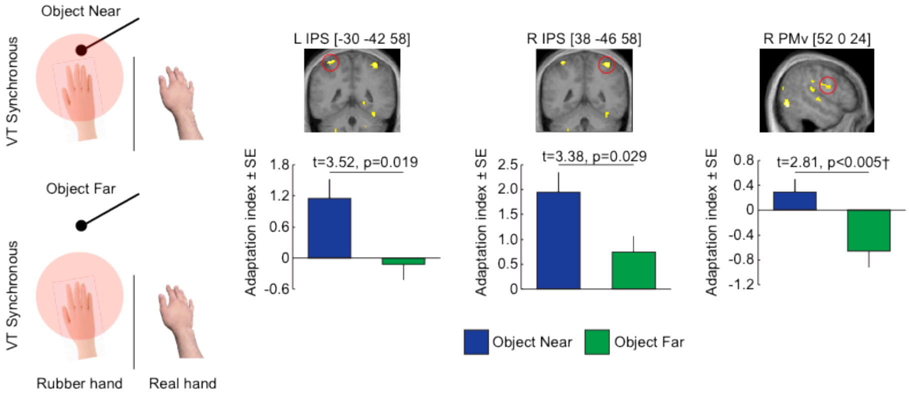

Figure 15. The perihand spatial remapping is restricted to the space close to, as opposed to far from, the embodied limb (unpublished data). Specifically, we found increased BOLD-adaptation to the presentation of an object close to, as opposed to far from, the artificial hand in the regions of the posterior parietal and premotor cortices identified before. † uncorrected for multiple comparisons.

Besides serving as an important replication of the behavioral and BOLD findings obtained in the main experiment, these additional findings have two main implications. First, they confirmed that the dynamic remapping of the perihand space representation to incorporate the artificial hand is selective to the space immediately surrounding the embodied artificial limb, as expected from the properties of the perihand visual RFs. Second, these findings ruled out the option that the BOLD-adaptation effects measured in the main experiments could be confounded by differences in the neural processing associated with the two different modes of visuo-tactile stimulation (synchronous vs. asynchronous) employed to elicit the illusion or to serve as control.

Taken together, the findings from Study IV characterize the hand-centered nature of the representation of the perihand space and relate this representation to the feeling of ownership and the sense of position of the hand. These findings also advance important questions for future studies. Arguably, the most relevant question refers to the causeand-effect relationships among the spatial position sense of the hand, the representation of the perihand space, and the feeling of ownership of the hand.

5.5 STUDY V: SELF-SPECIFIC MULTISENSORY PREDICTIONS IN THE HUMAN BRAIN

The aim of Study V was to test the hypothesis that the central representation of the hand forms self-specific multisensory predictions concerning incoming sensory signals. In order to create an experimental probe to gather evidence for this hypothesis, we investigated the BOLD responses evoked by the unexpected omission of a sensory stimulus (visual or tactile) to the hand. Such responses would reflect the violation of a multisensory expectation and, as a consequence, the existence of these multisensory predictions. To characterize the self-specific nature of these multisensory predictions, we adapted the setup based on the virtual reality tools used in Study II to change the self-attribution of the hand. This was achieved through the experimental manipulation of the congruence of the visual, tactile, and proprioceptive signals from the upper limb.

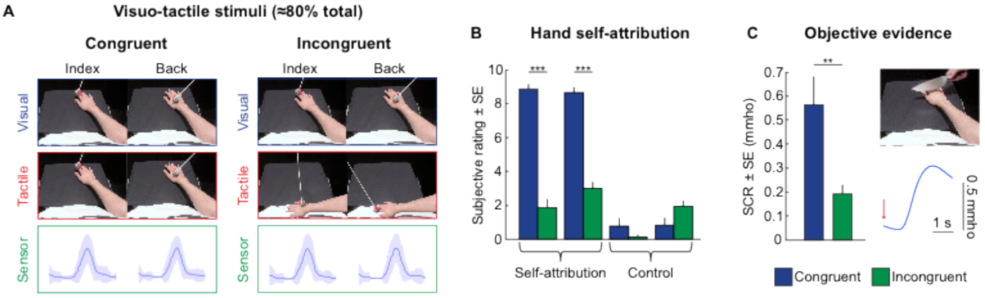

Figure 16. (**A**) Using a setup based on virtual reality, we manipulated the congruence of visual, tactile, and proprioceptive stimuli to the participants' right hand. Visuo-tactile stimuli represented approximately 80% of the events in each context (congruent vs. incongruent). (**B**) The participants experienced self-attribution of the hand only when the multisensory signals were congruent. ***$p<0.001$. (**C**) The changes in the self-attribution of the hand were confirmed by significantly greater threat-evoked skin conductance responses after periods of congruent, as opposed to incongruent, multisensory stimulation. **$p<0.01$.

This led to the design of two experimental contexts, one characterized by the vivid self-attribution of the seen hand, and the other by a significant reduction in the embodiment of the limb. In the former, the majority of the multisensory stimuli to the participants' hand were synchronous in time, congruent in space, and occurred within a match between the seen and felt postures of the hand. In the latter, the stimuli were synchronous in time but incongruent in space and in terms of the match between vision and proprioception, creating a conflict between the modalities that broke down the perception of the hand in view as one's own (Figure 16A).

As expected, the post-scan behavioral experiments confirmed the subjective and objective differences in the self-attribution of the hand between the two experimental contexts. Namely, the participants subjectively reported vivid self-attribution of the hand only in the context of congruence between the sensory signals (Figure 16B). This observation was further corroborated by the analysis of the threat-evoked skin conductance responses recorded during the fMRI sessions. In keeping with the subjective data, the psychophysiological recordings revealed stronger threat-evoked SCRs in the context of the self-attribution of the hand (Figure 16C).

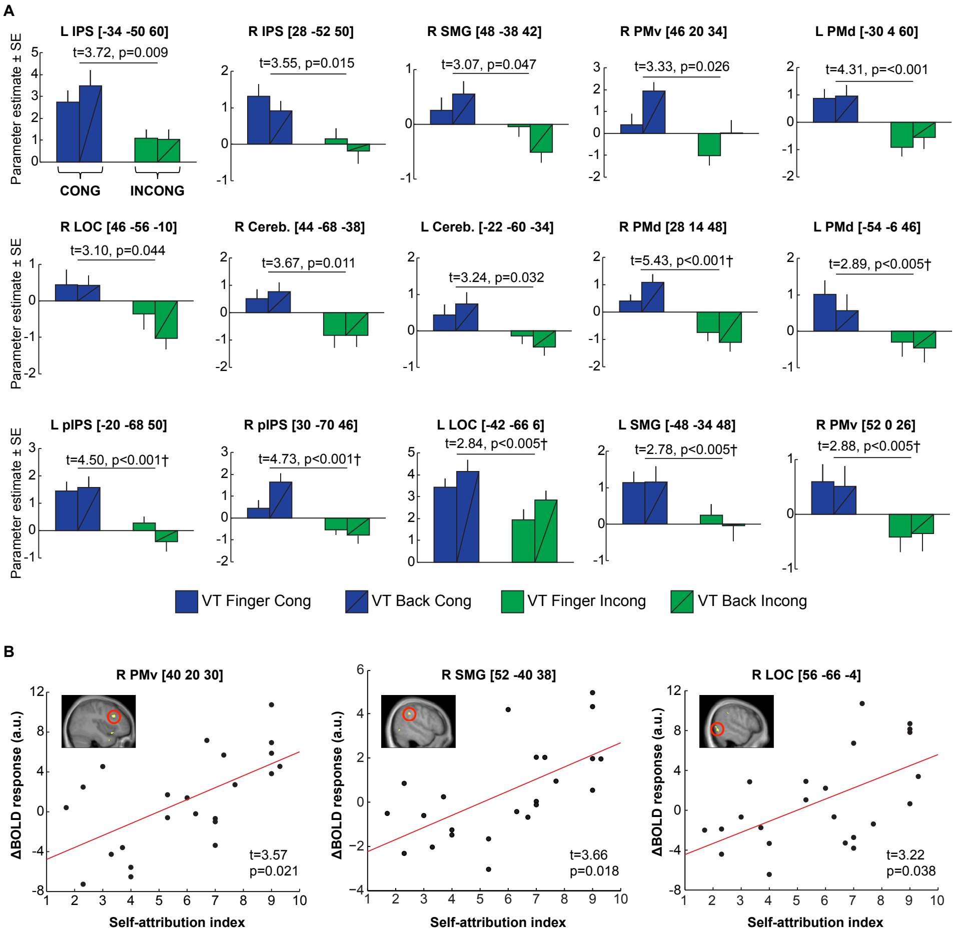

Figure 17. (**A**) The comparison of the BOLD responses to the congruent, as opposed to the incongruent, multisensory stimuli to the right hand revealed significant differences in frontal, parietal, and subcortical areas identified in the previous studies. † uncorrected for multiple comparisons. (**B**) The subjectively rated self-attribution of the hand was related significantly to the BOLD index of multisensory integration (congruent vs. incongruent) in key nodes of the multisensory areas described previously.

Moreover, the comparison of the BOLD responses evoked by the multisensory stimuli revealed stronger activations for the congruent, as opposed to the incongruent, visuo-tactile-proprioceptive stimuli. In agreement with the findings from Studies I and II, this response profile was observed in regions of the bilateral posterior parietal cortices, encompassing the intraparietal sulci and the supramarginal gyri, and in portions of the ventral and dorsal aspects of the bilateral premotor cortices (Figure 17A). Furthermore, an effect was found in the right and, at a lower threshold, in the left lateral occipito-temporal cortices. Subcortically, significant activations were found in the bilateral cerebellar lobes, and, at a lower threshold, in the bilateral superior collicula. The self-attribution index, derived from the subjective ratings, correlated positively with the BOLD index of multisensory integration (computed as the relative difference in activation between the two contexts) in regions of the premotor, inferior parietal, and lateral occipito-temporal cortices (Figure 17B). Taken together, the above findings corroborate the notion that the self-attribution of the hand changed significantly as a function of the relative congruence of the multisensory stimuli, as demonstrated by the converging neural, behavioral, and psychophysiological measures described above.

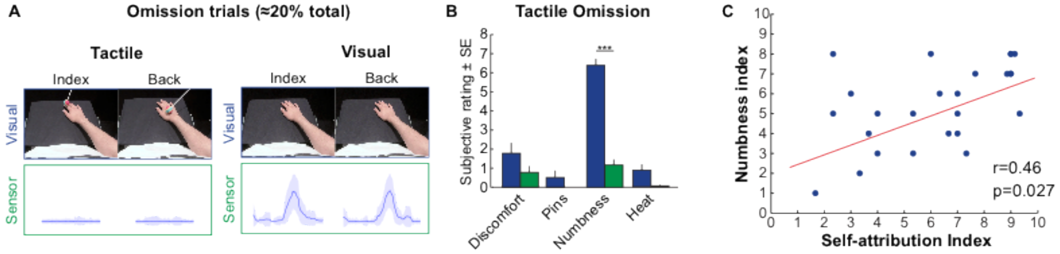

Figure 18. (**A**) To test the existence of self-specific multisensory predictions, we embedded unexpected omission trials in the experimental design, accounting for approximately 20% of the events in each context (congruent vs. incongruent). In the tactile omission trials, the tactile component of a visuo-tactile stimulus was unexpectedly omitted, whereas the opposite was true for the visual omission trials. (**B**) The unexpected omission of a self-specific tactile stimulus was associated with a feeling of numbness on the corresponding part of the hand***p<0.001 corrected. (**C**) We found that the stronger the self-attribution of the hand, the more intense the feeling of numbness associated with the omission of a tactile stimulus.

The key experimental manipulation consisted in the introduction of unexpected sensory omission in the two contexts of self-attribution of the hand. Embedded in the event-related experimental design, a minority of the stimuli in each context consisted of omission trials. In these, one of the components of the visuo-tactile stimulus was randomly omitted, either the tactile (tactile omission), or the visual (visual omission) component (Figure 18A). The occurrence of the omission trials was fully matched in terms of the type and the incidence across the two experimental contexts. Therefore, the only difference between the omission trials in the two contexts was the state of the self-attribution (present or absent) of the hand in which they occurred. Notably, the post-scan behavioral experiments revealed significant differences in the way the participants perceived the omission trials across the two contexts.

Interestingly, we found that the unpredictable occurrence of the tactile omission trials in the context of the self-attribution of the hand was associated with a feeling of numbness on the corresponding part of the hand, consistent with the existence of a self-specific somatosensory prediction originating from the appearance of the visual stimulus (Figure 18B). Interestingly, the subjective intensity of this feeling of numbness could be significantly predicted from the subjective strength of the self-attribution of the hand (Figure 18C). In other words, the stronger the feeling of ownership of the seen hand, the stronger the perceptual correlate associated with the sudden and unexpected violation of a self-specific visuo-tactile prediction. These results demonstrate a difference in the perception of the omission trials between the two contexts at the behavioral level, further investigated in the analysis of the BOLD responses evoked by the omission trials in the congruent and incongruent experimental conditions.

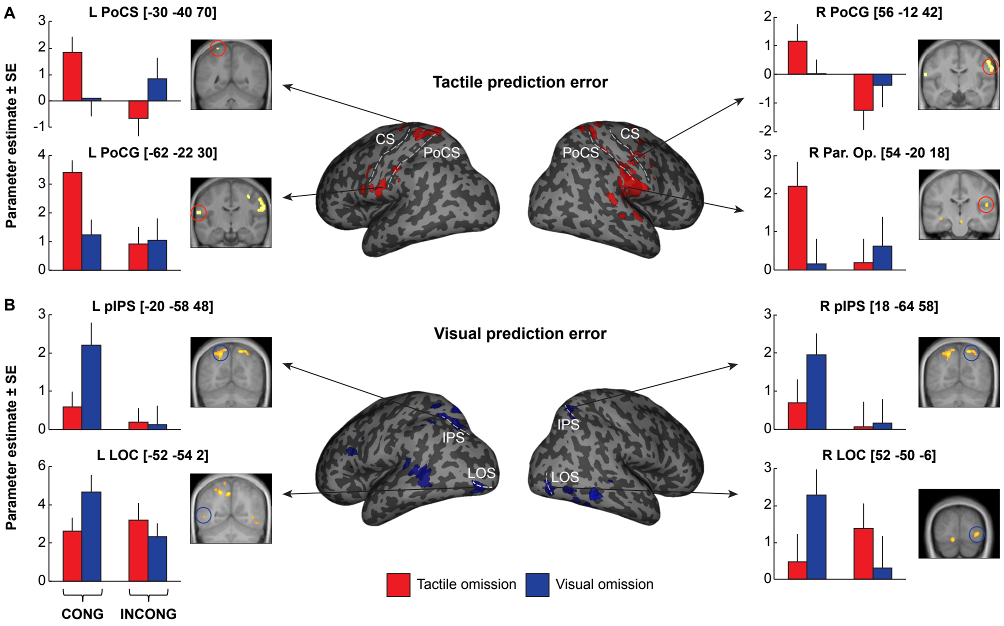

Figure 19. (**A**) The unexpected omission of a tactile stimulus to the hand evoked BOLD prediction error responses in regions of the bilateral somatosensory cortices, only when the hand was perceived as one's own in the context of multisensory congruence. (**B**) Conversely, the rare omission of a visual stimulus induced BOLD prediction error responses in regions of the posterior parietal and occipital cortices devoted to visual processing, only when the hand was self-attributed.

We hypothesized that the unexpected occurrence of the omission trials would lead to the generation of prediction error responses in the corresponding sensory cortices that signal the violation of multisensory-driven expectations. If such expectations differ between events that are self-attributed or not, then the corresponding prediction error signals should contain information concerning the self-specificity of the expectations. The analysis of the BOLD responses provided support for this hypothesis. The rare omission of an expected tactile event in the context of self-attribution of the hand was associated with increased BOLD responses in portions of the bilateral somatosensory cortices, encompassing parts of the postcentral gyri and sulci and the parietal opercula, as well as, subcortically, in the right cerebellum and in the left putamen (Figure 19A). Conversely, the omission of an expected visual event in the context of self-attribution of the hand, as opposed to the context of incongruent multisensory stimulation and reduced self-attribution of the hand, led to stronger BOLD responses in portions of the bilateral posterior intraparietal sulci and the lateral occipito-temporal cortices, together with a cluster in the left precuneus in the medial posterior parietal cortex and in the left lingual gyrus in the occipital lobe (Figure 19B). Both types of responses were selective to the context of self-attribution of the hand, suggesting the existence of self-specific, modality-oriented sensory predictions. Finally, we performed a conjunction analysis between the BOLD responses evoked by the omission of visual and tactile events specific to the context of self-attribution of the hand. This analysis revealed that the rare omission of an expected stimulus to one's hand, irrespectively of its sensory modality, was associated with increased activity in higher-order multisensory areas of the posterior parietal, inferior parietal, and premotor cortices. This finding is consistent with the notions that the prediction error signals in the early sensory cortices interact with the neuronal processing in the higher levels of the cortical hierarchy that construct the dynamic multisensory representation of the hand.

Two multiple regression analyses indicated that the magnitude of the prediction error responses described above were proportional to the subjectively rated self-attribution of the hand, in a fashion that was both self-specific and modality-specific. In other words, the tactile prediction error signal in somatosensory areas mirrored the self-attribution of the hand. Conversely, the strength of the self-attribution of the hand was related to the visual prediction error signals in regions of the posterior parietal cortex (Figure 20). In conclusion, the fMRI analyses followed on the tracks of the behavioral findings and suggested the existence of self-specific multisensory predictions via the detection of omission responses to rare violations of these predictions.

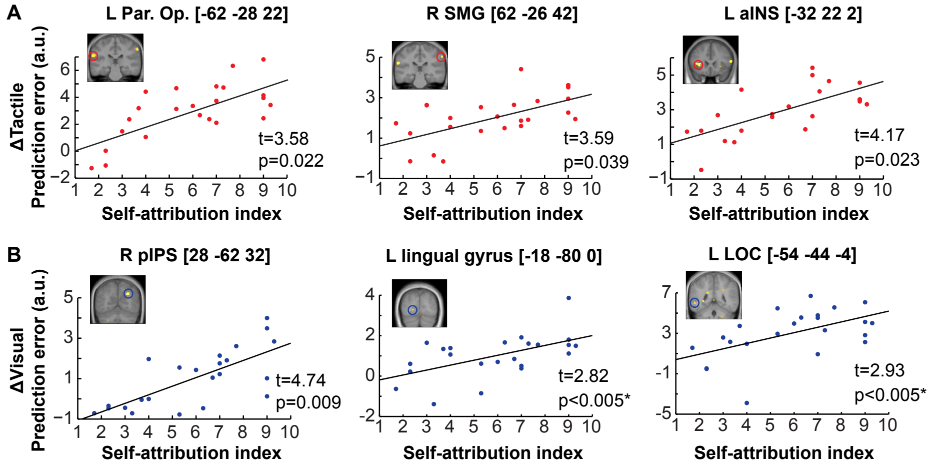

Figure 20. (**A**) The self-attribution of the hand was significantly related to the magnitude of the BOLD prediction error responses to the omission of a self-specific tactile stimulus to the hand in regions of the somatosensory, inferior parietal, and anterior insular cortices. (**B**) Instead, the self-attribution of the hand mirrored the amplitude of the BOLD prediction error signals to the unexpected omission of self-specific visual stimuli to the hand in regions of the posterior parietal and occipital cortices. *uncorrected.

Taken together, the findings from Study V support the hypothesis that the central multisensory representation of the hand generates self-specific predictions concerning incoming sensory signals. The results suggested the involvement of both primary and secondary early sensory areas and higher-order multisensory regions in the association cortices. This fits with the notion that the neuronal processing of sensory stimuli to one's own hand is dynamically related to the interplay between different levels of the cortical hierarchy. These preliminary findings raise important questions for future experiments, including the functional role of the multisensory prediction error signals, the exact nature of the predictions that are formed by the higher-order association areas, and the dynamics of the interplay between the different levels of the cortical hierarchy.

6 GENERAL DISCUSSION

This section aims at bringing together the main findings of the studies presented in the thesis in a general, overarching interpretation of their relevance to the investigation of the mechanisms underpinning the neural representation of the hand and the perihand space. For in-depth discussion of the findings from each study, the reader is referred to the preceding Results section, as well as to the attached articles and manuscripts. Further relevant findings are also factored in to extend the main conclusions and help identify outstanding open questions and relevant directions for future research.

6.1 THE MULTISENSORY REPRESENTATION OF THE HAND

A major aim of the studies included in the thesis was to gather evidence for a central multisensory representation of the hand that draws from the integration of congruent visual, tactile, and proprioceptive signals from the upper limb. Moreover, we collected complementary behavioral, psychophysiological, and BOLD measures to support the notion that this multisensory representation might be related to the multifaceted self-perception of the hand itself. Using a combination of ecologically valid experimental setups and sensory stimuli, as well as setups based on virtual reality tools, we obtained consistent evidence for the convergence of multisensory signals from the upper limb in regions of the posterior parietal and premotor cortices, as well as in subcortical structures like the cerebellum and the putamen. In these regions, the BOLD responses evoked by visuo-tactile stimuli applied to the participants' right hand carried linear and non-linear signatures of multisensory integration, and they were sensitive to the congruence of the sensory inputs, including matching visual and proprioceptive signals concerning the position of the hand. The neuroanatomical and functional characteristics of the findings were consistent with the earlier neurophysiological evidence in non-human primates and the neuropsychological, behavioral, and neuroimaging studies in humans recapped in depth in the Introduction.

Despite the caution that must be exercised when drawing homologies between brain regions in the non-human primate and human brains (especially with respect to the fronto-parietal association cortices; Bremmer et al., 2001; Grefkes et al., 2002; Grefkes and Fink, 2005; Culham et al., 2006), the anatomical locations of the candidate brain regions that combine visual, tactile, and proprioceptive signals to build a multisensory representation of the hand fit well with the neurophysiological data in monkeys, as well as with the neurological observations in patients suffering from brain damage resulting in impairments in the multisensory representation of the body. Two brain regions of particular interest are the posterior parietal cortex and the premotor cortex, whose well-known role in assisting key behavioral functions is examined in the following sections.

The fMRI experiments reported consistent peaks of activations located in the intraparietal sulcus and in regions of the superior and inferior parietal lobes that are separated by this sulcus. Neurophysiological research in non-human primates has characterized multiple subdivisions of the cortex lining the intraparietal sulcus, including anterior (AIP), ventral (VIP), medial (MIP), and lateral (LIP) partitions, each with a set of well-defined receptive field properties and functions (Colby and Duhamel, 1991; Luppino et al., 1999; Grefkes and Fink, 2005; Culham et al., 2006). Because of the difficulties in establishing homological relations, we labeled the activation peaks found in the fMRI experiments based on their location relative to clearly identifiable anatomical landmarks (see for reference the atlas of Duvernoy and Parratte, 1999). For instance, we regularly employed the label “anterior intraparietal sulcus” (aIPS) to describe activation peaks located in the anterior segment of the intraparietal sulcus, often in the vicinities of the junction with the posterior bank of the postcentral sulcus. This label should not be confused with the label AIP used for non-human primates. Nevertheless, as remarked before, the neuroanatomical distribution of the findings from the fMRI experiments presented in the thesis fits well with the distribution of neuronal populations with similar properties in monkeys. These areas included peaks in the supramarginal gyrus, possibly corresponding to inferior parietal area 7b/PF in monkeys (Hyvärinen and Poranen, 1974; Krams et al., 1998), parts of the postcentral sulcus and the superior parietal lobule suggestive of the analogous areas 2 and 5 in monkeys (Sakata et al., 1973; Graziano et al., 2000), portions of the precentral gyri and precentral and inferior frontal sulci (PMv and PMd; see areas F2, F4, F5, and F7 in the monkey's frontal lobe; Graziano and Gandhi, 2000; Luppino and Rizzolatti, 2000), the cerebellar hemispheres (Dum and Strick, 2003; Sultan and Glickstein, 2007), and in the putamina (Graziano and Gross, 1993). As described in detail in the Introduction, the above regions of the monkey’s brain contain multisensory neurons that are responsive to congruent sensory inputs to the limb and that support a hand-centered representation of the perihand space (see next section). Hence, the above considerations entail that the multisensory representation of the hand in humans investigated with fMRI bears remarkable neuroanatomical and functional similarity to the representation of the upper limb in non-human primates.

A remarkable advantage associated with the performance of neuroimaging experiments in healthy humans is the possibility to relate measures of brain activity to a variety of indicators that reflect psychological phenomena such as the self-perception of one's own hand. In the experiments presented in the thesis, we capitalized on this advantage by deploying a battery of subjective and objective means to quantify different aspects of the self-perception of the hand, such as the feeling of ownership of the hand and the perceived position of the upper limb.

Throughout all of the experiments, we found evidence in support of the hypothesis that the feeling of ownership of the hand is contingent upon the congruence of visual, tactile, and proprioceptive inputs from the upper limb. Even when presented with a 3D image of their own right hand see through the head-mounted displays, the participants in our experiments reported a vivid percept of the seen hand as their own only in the context of congruence between the multisensory signals. These subjective reports were bolstered by the observation that threats directed toward the hand led to differential psychophysiological and BOLD responses that echoed the feeling of ownership of the hand. Moreover, these subjective and objective indices of self-attribution mirrored the changes in the BOLD signal in key premotor and parietal nodes of the circuits that support the multisensory representation of the hand outlined above. These findings provide support for the hypothesis that the multisensory representation of the hand, constructed with the help of the integration of congruent sensory signals from the upper limb and the space around it (see next section for further discussion on the representation and role of the perihand space), might lead to the emergence of the feeling of ownership of the hand. This contributes significantly to current accounts of bodily self-perception that associate multisensory mechanisms in the regions of the parietal and premotor cortices described above to the self-attribution of the limb (see Makin et al., 2008; Tsakiris, 2010; Blanke, 2012; Ehrsson, 2012 for recent reviews). Support to these models has been hitherto derived almost exclusively from studies linking the illusory ownership of artificial limbs (Ehrsson et al., 2004, 2007; Tsakiris et al., 2007) to brain activity in the multisensory frontal, parietal, and subcortical regions described above. However, these studies cannot fully rule out the contribution of factors that might be inherently tied to the (often unusual) experience of perceptual illusions of ownership of non-corporeal objects, such as attentional arousal, task demands, visuo-proprioceptive spatial recalibrations, and so forth (Botvinick, 2004; Moseley, 2011). In light of this, the findings that the integration of multisensory stimuli to one's own hand, particularly with the use of an ecologically valid experimental setup in the absence of spatial recalibrations, unusual illusory sensations, complex and/or indirect vision (such as via mirrors or setups based on virtual reality technology), or task-related effects, results in the robust engagement of specific premotor, posterior parietal, and subcortical brain regions provides key support to models of bodily self-perception (Makin et al., 2008; Tsakiris, 2010; Blanke, 2012; Ehrsson, 2012).

It is important to bear in mind that, despite the converging evidence from neural, behavioral, and psychophysiological measurements, the experiments discussed here do not provide any information on the spatio-temporal dynamics and on the causal role that the different neural nodes of the multisensory representation of the hand play in supporting the self-perception of the limb. Interpreted against the background of neurophysiological studies in non-human primates and behavioral and neuroimaging research in humans, our findings contribute to the pool of knowledge that can guide future research with techniques like electroencephalography, electrocorticography, and transcranial magnetic stimulation. These methodologies have the potential to build on early neuroimaging and neuropsychological findings in order to significantly advance our understanding of the causal mechanisms.

The investigation of the multisensory neural representation of the hand and its role in supporting the self-perception of the limb are also of relevance to current theoretical accounts that attempt to contextualize models of bodily self-perception within broader theories of perception, such as those anchored on the notion of predictive coding (see Introduction, as well as Rao and Ballard, 1999; Apps and Tsakiris, 2013; Clark, 2013; Limanowski and Blankenburg, 2013; Seth, 2013 for recent reviews). These theories posit that the self-perception of one's body emerges from the dynamic interplay of prior knowledge and bottom-up sensory signals that are constantly being compared with each other. Hence, one of the principal tenets of these theories is the concept that the neural representation of the body in the association cortices forms multisensory predictions concerning incoming sensory signals. Similarly, these theories postulate that the neural processing in primary and secondary sensory areas reflect the dynamic comparison of the afferent inputs to their prior expectations, which in turn generates prediction error signals that reflect the degree of deviation between predictions and inputs. These sensory prediction errors can then be employed by higher-order areas to dynamically update the multisensory representation of the hand and the associated predictions concerning incoming stimuli. This constant interplay between predictions and afferent inputs appears to be ideally suited to support the self-specific processing of sensory signals generated or received by one's body (Blakemore et al., 1998; Seth et al., 2011; Apps and Tsakiris, 2013). Despite the theoretical appeal of the extension of predictive coding principles to existing models of bodily self-perception, experimental support is meager, especially with respect to neuroimaging data.

Importantly, we provided preliminary experimental support for the hypothesis that the multisensory representation of the hand forms self-specific predictions concerning incoming sensory events. Specifically, we measured BOLD responses to unexpected omissions of a sensory event that were consistent with the generation of a prediction error signal in response to a violation of prior multisensory expectations. These BOLD responses were specific to the context of self-attribution of the hand, they reflected the modality-specific nature of the violation of existing multisensory predictions, and they scaled with the subjectively rated self-attribution of the hand. Intriguingly, we also found preliminary evidence for a measurable perceptual correlate of the violation of these self-specific predictions. Namely, we discovered that the unexpected omission of a tactile event, predicted from a congruent visual stimulus approaching the hand in the context of self-attribution of the hand, was associated with a feeling of numbness on the corresponding part of the hand, as reported subjectively by the participants in our fMRI experiments. Conversely, in the condition in which the majority of the multisensory stimuli were incongruent, the self-attribution of the hand lessened significantly and the (equally rare and unexpected) omissions did not evoke prediction error responses with self-specific information. In conclusion, these preliminary findings offer encouraging backing to the notion that the self-attribution of the hand is associated with the interplay between higher-order self-specific multisensory predictions and afferent sensory inputs. However, much remains to be investigated concerning this theoretical account. The experiments presented here did not submit any evidence for the mechanisms that might support this interplay, nor did they inform us on the precise nature of these self-specific multisensory predictions. The inherent limitations of fMRI did not permit any conclusion to be drawn regarding the spatio-temporal dynamics associated with the generation and the processing of these prediction and prediction error signals, respectively. New studies also need to address the central issue of how the multisensory neural representation of the hand takes into account prediction error signals to update, if required, its prior expectations concerning the sensory environment.

In summary, the experiments presented in the thesis characterized multiple aspects of the central multisensory representation of the hand. Using fMRI, we put forward that neuronal populations in anatomically connected frontal, parietal and subcortical areas integrate congruent multisensory stimuli from the hand. The RF properties of these neuronal populations allow them to integrate tactile stimuli to the hand with spatio-temporally congruent visual stimuli within the perihand space (see next section). Furthermore, the convergence of proprioceptive inputs onto these neuronal populations anchors the visuo-tactile integrative mechanisms to a reference frame centered on the upper limb. Using complementary behavioral and physiological measurements, we proposed that the perceived ownership of the hand is intimately related to the neuronal mechanisms responsible for the construction of the multisensory representation of the hand. Within this framework, a vivid sense of ownership of the hand and a coherent central multisensory representation of the limb are, arguably, essentially equivalent. Finally, we obtained preliminary evidence in support of the notion that the link between the multisensory representation of the hand and the self-perception of the hand itself might be extended and sophisticated to include the interplay of prior multisensory expectations concerning self-specific sensory events and the processing of afferent sensory inputs. The above observations are associated with a number of outstanding open questions that should be the object of future studies.

6.2 THE PLASTIC REPRESENTATION OF THE PERIHAND SPACE

One of the major aims of the experiments presented in this thesis was to provide neuroimaging evidence for a representation of the space immediately surrounding the hand, or perihand space, that is spatially anchored to the upper limb. Using ecologically valid stimuli and a sensitive analysis technique, we gathered evidence that suggests the existence of neuronal populations in frontal, parietal, and subcortical areas with visual RFs properties that are ideally suited to support such a representation. Furthermore, the effect of proprioceptive inputs from the arm onto these neuronal populations allows the spatial remapping of the visual RFs, yielding a representation of the perihand space that is anchored to the upper limb (Graziano et al., 2000). These results are in keeping with the literature in non-human primates and the neuropsychological and behavioral research in humans reviewed in depth in the Introduction (see Introduction and Results, as well as the included articles and manuscripts, for extensive details). Of special interest to the present general discussion are related findings that further extend our knowledge of the functional properties of the representation of the peripersonal space. In particular, the following paragraphs examine two interesting aspects of this representation: its “mirror-like” properties that were the focus of a recently published study (Brozzoli et al., 2013), and its inherent functional plasticity, as exemplified by the observation of the effects of limb amputation and the use of tools.

In a recent series of experiments, we employed the BOLD-adaptation paradigms described in Studies III and IV to test the hypothesis that the neural representation of the perihand space might extend to represent the space around another person’s hand (Brozzoli et al., 2013), in a manner analogous to the seminal description of visuo-motor mirror neurons in the brain of non-human primates and humans (di Pellegrino et al., 1992; Rizzolatti and Craighero, 2004; Caggiano et al., 2009; Kilner et al., 2009; Mukamel et al., 2010). Moreover, this hypothesis was also predicated on a recent study that described visuo-tactile neurons in the monkey’s posterior parietal cortex with mirror properties, i.e. visuo-tactile neurons that are also responsive to stimuli delivered to the corresponding body part of another individual (Ishida et al., 2010). In two separate fMRI experiments involving forty-six healthy volunteers, we identified a region in the human left ventral premotor cortex that encodes the presence of an object in both the space around one’s own hand and the space around the hand of another individual (Brozzoli et al., 2013). This effect was specific to another person’s hand, as opposed to an artificial humanoid hand, was restricted to the perihand space of the participant’s and the other person’s hand, and was independent of the spatial location of the other’s hand, i.e. exhibited hand-centered properties (Figure 21).

What is the putative role of this shared representation of the perihand space? We put forward that this specific property might serve as the basic mechanism providing the brain with a common spatial reference frame that encodes the presence of objects in the vicinity of one’s own hand and of the hand of other individuals in the environment (Brozzoli et al., 2013). In turn, this basic mechanism might help coordinate complex social behaviors that involve interactions with others. These results are important as they point to an avenue for future research that may bridge the basic mechanisms under investigation in the thesis with the research on the foundations of socially relevant behaviors (Heed et al., 2010; Brozzoli et al., 2013; Teneggi et al., 2013).

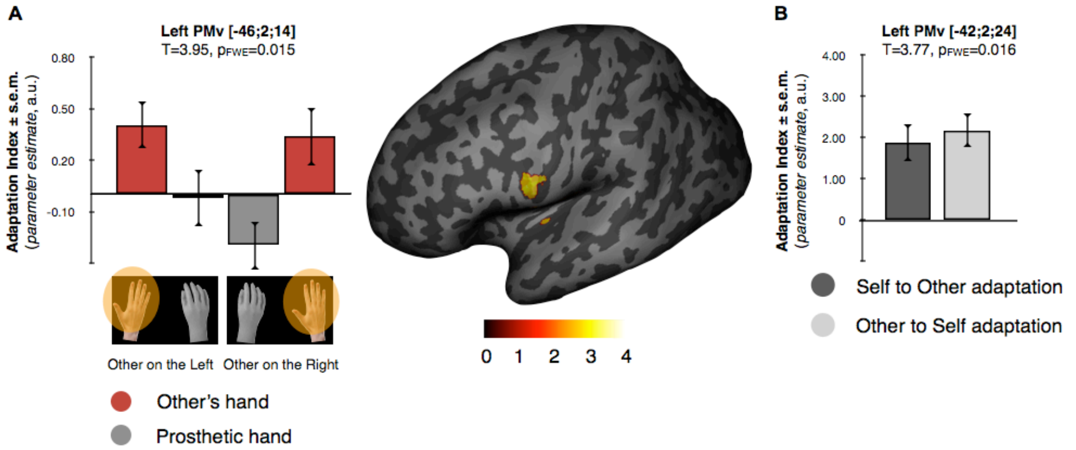

Figure 21. The representation of the perihand space in the ventral premotor cortex is also selective to visual stimuli presented in the perihand space of another individual (Brozzoli et al., 2013). (**A**) We found increased BOLD-adaptation in the left ventral premotor cortex to the presentation of an object in the vicinity of another person's hand, as opposed to an artificial hand, regardless of the absolute spatial location of the hand. (**B**) The BOLD-adaptation effect was bidirectional, further corroborating the nature of the shared representation of the perihand space in the ventral premotor cortex.

Valuable insights on the properties of the representation of the perihand space come from the investigation of the consequences of the amputation of the upper limb. The majority of amputees report an array of sensations associated with the experience of their missing limb, indicated by the umbrella term "phantom limb" experiences, the most clinically relevant of which is the "phantom pain" associated with the missing limb (Flor et al., 1995; Ramachandran et al., 1995; Ramachandran and Hirstein, 1998; Ehrsson et al., 2008; Schmalzl and Ehrsson, 2011; Makin et al., 2013). What happens to the representation of the perihand space following the loss of the upper limb? In a recent study, Makin and colleagues (Makin et al., 2010) described how amputees suffer from symptoms resembling those related to spatial neglect (Halligan and Marshall, 1991; Jacobs et al., 2012; Karnath and Rorden, 2012), limited to the space surrounding the stump. These findings are compatible with the idea that the loss of the limb limits the range of potential interactions with objects in the corresponding part of space, thereby affecting the representation of the perihand space in a manner that is consistent with its function as a sensorimotor interface (Makin et al., 2010; see next section). Similarly, a study by Canzoneri and colleagues described how the loss of the limb leads to a contraction of the spatial boundaries of the perihand space, an effect that was partly reversed by the use of a prosthesis (Canzoneri et al., 2013). These results shed light on the properties of the perihand space representation by informing us on how limb amputation reshapes it.

What evidence other than the effects of the amputation of the upper limb points to the inherent plasticity of the representation of the perihand space? A fruitful line of research has focused on the use of tools, an essential ability to extend the repertoire of possible interactions with objects in the environment (Iriki et al., 1996; Berti and Frassinetti, 2000; Maravita and Iriki, 2004; Culham and Valyear, 2006; Cardinali et al., 2009b; Valyear et al., 2012). Neurophysiological research in non-human primates and behavioral and neuroimaging studies in humans have suggested that dexterous tool use might be supported by parts of the neural infrastructure in place to integrate sensory signals from the body and the peripersonal space (Iriki et al., 1996; Johnson-Frey, 2004; Maravita and Iriki, 2004; Farnè et al., 2005; Culham and Valyear, 2006; Bonifazi et al., 2007; Làdavas and Serino, 2008; Cardinali et al., 2009b). However, the ability to use tools also entails access to specific knowledge related to the properties, functions, and previous experience with tools (Johnson-Frey, 2004; Culham and Valyear, 2006; Valyear et al., 2012). In essence, the functional use of tools extends the repertoire of possible interactions with objects in what would otherwise be extrapersonal, out-of-reach space. However, the exact nature of the plastic reshaping of the perihand space representation induced by tool use is the object of experimental debate (see for example Holmes, 2012). The BOLD-adaptation experiments described in this thesis could be readily adapted to contribute to such debate (Bekrater-Bodmann and Foell, 2013).

The above considerations significantly enrich the account of the basic mechanisms underpinning the multisensory representation of the perihand space provided by the studies included in the thesis. This representation is multifaceted: it is linked to the localization and self-attribution of the hand, it possesses mirror-like properties, and it is affected by the loss of the upper limb and, possibly, by the use of tools. However, much remains to be investigated concerning the neural representation of the perihand space. An outstanding open question relates to the spatial extent of this representation in humans. The BOLD-adaptation data presented in the thesis suggest that the visual RFs of the neuronal populations that are responsive to an object in the vicinity of the hand are limited in their spatial extent. These data also suggest that the perihand space representation is distinct from a representation of the reaching space (see in particular

Study IV). In all the experiments, changes in the relative distance between the position of the participant's hand and the three-dimensional object were always confined within the boundaries of the participants' reaching space. Nevertheless, we consistently found evidence in support of the existence of neuronal population with visual RFs that are selective to the presence of an object in the immediate vicinity of the hand, as opposed to objects farther from the hand but still within the limits of reaching space. This points to a distinction between the representation of the perihand space under investigation here and a more general representation of objects within reach of the hands. However, no neuroimaging evidence is available to date that informs us on the spatial extent of the perihand space representation. The perihand visual RFs described in non-human primates typically extend up to a distance of roughly 30 cm (in a few cases, up to 1 m) from the location of the corresponding tactile RFs (Rizzolatti et al., 1981a, 1981b; Graziano et al., 1997). Moreover, neuropsychological and behavioral studies in humans seem to converge on a spatial boundary located roughly 30 to 45 cm from the body surface (Làdavas et al., 1998; Farnè et al., 2003; Lloyd, 2007; Makin et al., 2009; Canzoneri et al., 2012). These observations indicate the need for future research to provide an in-depth characterization of the visuo-tactile RFs associated with the neuronal populations that represent the perihand space.

6.3 A MULTISENSORY INTERFACE FOR DEFENSIVE AND GOAL-DIRECTED ACTIONS

The findings from the experiments presented in the thesis converged to corroborate the existence of a multisensory representation of the hand and the immediate space around it, in keeping with data from neurophysiological investigations in non-human primates, and neuropsychological and behavioral research in humans. Complementary behavioral, psychophysiological, and BOLD measures further supported the hypothesis that these multisensory mechanisms lead to the emergence of the feeling of ownership of the hand. From an evolutionary perspective, the role of these multisensory processes in supporting the self-perception of the hand is, arguably, secondary to the development of their contribution to essential behavioral functions (Graziano and Botvinick, 2002; Fogassi and Luppino, 2005; Brozzoli et al., 2012; Makin et al., 2012). However, none of the experiments in the thesis provided data that link the multisensory representation of the hand and the perihand space to the planning and performance of essential goal-directed behaviors. Rather, they provided insights on the role of basic multisensory integrative mechanism in supporting the central representation of the hand. In turn, this neural infrastructure may support the well-known sensorimotor functions of the frontal, parietal, and subcortical brain regions involved in the performance of goal-directed actions. In the following paragraphs, the main findings from the experiments included in the thesis are contextualized within the literature covering the investigation of the essential sensorimotor functions that rely on the integration of signals from the hand.

As mentioned previously, an evolutionarily compelling account of the development of the multisensory representation of the body and the peripersonal space emphasizes its role in the protection of the body from potential threats, an essential requirement for survival (Graziano and Botvinick, 2002; Cooke et al., 2003; Graziano and Cooke, 2006). Namely, the body-part-centered representation of the peripersonal space allows the brain to encode the location of a potential threat in a spatial coordinate system that takes the body itself as the reference. The multisensory receptive fields of the neuronal populations in frontal, parietal, and subcortical areas combine visual inputs with tactile and proprioceptive information to form accurate predictions concerning the potential impact zone on the body surface (Colby et al., 1993a; Duhamel et al., 1998; Rind and Simmons, 1999; Avillac et al., 2005). In turn, this information is employed to rapidly plan and perform the sequence of movements required to dodge a harmful object and protect the body from the associated threat. Indeed, the electrical stimulation of multisensory neurons in the non-human primate brain initiates complex movement sequences that are compatible with defensive actions (Cooke and Graziano, 2003; Cooke et al., 2003; Graziano and Cooke, 2006). In behavioral studies in humans, the defensive role of the representation of the peripersonal space has also been emphasized. Using transcranial magnetic stimulation, Makin and colleagues described how the entrance of a potentially harmful object in the perihand space leads to changes in the corticospinal excitability that are compatible with the automatic generation of defensive motor sequences (Makin et al., 2009, 2012). Similarly, the studies of Sambo and others have linked reflexive defensive actions to the processing of sensory stimuli in the peripersonal space (Sambo et al., 2012a, 2012b; Sambo and Iannetti, 2013). Our results fit with the basic mechanisms described above. Specifically, we found multisensory neuronal populations in posterior parietal, premotor, and subcortical areas with visual RFs properties that are suitable to carry out the computations required to plan defensive movements. These neurons have visual RFs limited to the perihand space and spatially anchored to the hand, potentially facilitating the rapid translation of the visual inputs concerning a potential threatening object into hand-centered coordinates. Moreover, we found that threats directed toward the hand evoked selective BOLD responses in regions of the premotor and cerebellar cortices. Speculatively, these responses might reflect the engagement of automatic defensive reactions aimed at protecting the hand from the incoming threat. Moreover, the multisensory properties of the central representation of the hand inferred from the work presented in the thesis fit well with the idea that this representation allows the formation of accurate predictions concerning incoming stimuli. As remarked above, these predictions are essential in guiding defensive movements in response to potentially harmful objects. Future research along these lines should focus on determining whether the multisensory neuronal populations identified in the present experiments possess the sensorimotor properties required to coordinate defensive movements, in keeping with the neuropsychological data in non-human primates and the behavioral research in humans reviewed above.

Besides coordinating defensive actions, the multisensory representation of the hand and the perihand space is ideally suited to act as an interface for essential goal-directed actions (Jeannerod et al., 1995; Andersen et al., 1997; Ehrsson et al., 2000; Luppino and Rizzolatti, 2000; Rizzolatti and Luppino, 2001; Culham and Valyear, 2006). The apparent simplicity of goal-directed movements such as reaching for and grasping a piece of food belies the complexity of the sensorimotor transformations required for their successful completion. For example, these simple goal-directed movements require the dynamic coordination of the eyes and the hands as the action unfolds in time (Andersen et al., 1997; Johansson et al., 2001; Crawford et al., 2004; Fogassi and Luppino, 2005; Culham and Valyear, 2006). This relies on the complex interplay between distinct spatial reference frames, such as those centered on retinal coordinates that encode the location of a target object, and those centered on the motor effectors that partake in the action (Andersen et al., 1997; Graziano, 2001, 2006; Culham et al., 2006; Pesaran et al., 2006; Andersen and Cui, 2009). A vast literature consisting of both neurophysiological studies in monkeys and research in humans has tackled the complex issue of the spatial reference frames employed in the coordination of goal-directed actions (Jeannerod et al., 1995; Battaglini et al., 1996; Andersen et al., 1997; Graziano, 2001; Culham et al., 2003, 2006; Galletti et al., 2003; Fogassi and Luppino, 2005; Fattori et al., 2009). Our findings contribute significantly to this topic by offering neuroimaging evidence for a spatial reference frame centered on the upper limb, in neuroanatomical and functional agreement with the literature mentioned above. The multisensory representation of the hand characterized in the thesis is well suited to support goal-directed actions by providing the sensorimotor programs with critical sensory data required to plan and execute the action (Andersen et al., 1997; Culham and Kanwisher, 2001; Grefkes and Fink, 2005).

As remarked above, the existence of a multisensory representation of the hand in fronto-parietal areas is consistent with the known role of these regions in translating visual and tactile signals from the hands and from the target object into the required motor plan to for successful interactions (Jeannerod et al., 1995; Ehrsson et al., 2000; Culham and Valyear, 2006; Johansson and Flanagan, 2009). Neuroimaging evidence in humans, for example, has followed on the tracks of neurophysiological research in non-human primates to emphasize the role of the posterior parietal cortex in processing the inputs from the hand and from the target object required for reaching and grasping actions, such as the size, shape, and relative position of the target object with respect to the eyes and the hands (Ehrsson et al., 2000; Culham et al., 2003; Grefkes and Fink, 2005; Culham and Valyear, 2006; Rice et al., 2007; Króliczak et al., 2008; Naito et al., 2008; Bernier and Grafton, 2010; Cavina-Pratesi et al., 2010). Furthermore, neurophysiological research in patients suffering from damage to the posterior parietal lobes has emphasized the essential role of areas like the anterior intraparietal sulcus in guiding hand-object interactions (Binkofski et al., 1998; Grefkes and Fink, 2005; Karnath and Perenin, 2005; Pisella et al., 2009). Our results fit well with these notions by characterizing the convergence of visual, tactile, and proprioceptive signals from the hand in the regions of the posterior parietal cortex found consistently in the literature cited above. Again, the visual RFs of the neuronal populations identified in these areas are ideally suited for the encoding of the position of an object in hand-centered coordinates, one of the key passages in the sensorimotor transformations required for hand-object interactions. Despite the remarkable neuroanatomical similarities between the representation of the hand and the perihand space presented in the thesis and the well-known brain circuits that utilize multisensory signals from the hand to guide relevant behavior, we did not provide any experimental support to probe their functional connection (or possibly their equivalence). This represents an observation of major relevance for future research. Indeed, neuroimaging paradigms that combine the basic multisensory effects described in the thesis could be integrated with the investigation of defensive and goal-directed actions performed in the perihand space, whereas techniques like transcranial magnetic stimulation could be employed to shed light on the causal role of the fronto-parietal nodes of the multisensory representation of the hand and the perihand space.

6.4 THE CONTRIBUTION OF INTEROCEPTIVE SIGNALS

The studies presented in the thesis, as well as the other relevant studies that have hitherto contributed to the general discussion, have concentrated on the role that visual, tactile, and proprioceptive signals take in the construction of a representation of the hand and the perihand space. However, the theoretical and experimental accounts that portray the neural mechanisms supporting the integration of multisensory signals from the body would fall short of being comprehensive if they didn't embrace a whole class of sensory inputs that constantly reach the brain carrying information about the current physiological state of the body. These sensory inputs, sometimes referred to as interoceptive (Craig, 2003), convey information such as temperature, pain, visceral, vascular and other physiological sensations, and sensory information loaded with emotional content, such as pleasant touch (Björnsdotter et al., 2010; Olausson et al., 2010; Craig, 2011; Morrison et al., 2011). Interoceptive signals converge onto cortical regions such as the insular complex (Craig, 2003, 2011; Björnsdotter et al., 2009; Olausson et al., 2010), where they can be combined with exteroceptive signals to construct a representation of the body that draws from both interoceptive and exteroceptive signals, accounting for the multifaceted range of sensory experiences associated with the self-perception of one's body (Craig, 2002, 2010; Tsakiris et al., 2007; Tsakiris, 2010; Seth, 2013).

Recent behavioral studies have attempted to address the issue of how interoceptive signals interact with exteroceptive signals in the induction of illusory experiences of bodily self-perception. For example, the degree of awareness over one's own heartbeat (Tsakiris et al., 2011) and the felt pleasantness of touch (Crucianelli et al., 2013) have been shown to interact with the integration of visual, tactile, and proprioceptive signals that leads to the induction of the rubber hand illusion. In spite of the recent upsurge in theoretical accounts linking the integration of interoceptive and exteroceptive signals to the self-perception of one's body (Craig, 2010; Apps and Tsakiris, 2013; Limanowski and Blankenburg, 2013; Seth, 2013), little is known about the associated multisensory neural mechanisms. As clarified previously, the experiments presented in the thesis focused on the contribution of the multisensory integration of exteroceptive inputs from vision, touch, and proprioception in constructing a representation of the hand that might support the self-perception of the hand itself. The threat-evoked psychophysiological and BOLD responses tapped into the array of emotional experiences associated with the self-perception of one's own body. However, the present studies were not informative about the putative neural mechanisms whereby these exteroceptive inputs interact with interoceptive signals in constructing the multisensory representation of the body. This question represents an important direction for future research: experimental designs that both manipulate the emotional value of visuo-tactile stimuli and factor in interoceptive signals related to the psychophysiological state of the body might help shed light on the neural mechanisms discussed above.

6.5 BEYOND THE HAND: THE MULTISENSORY REPRESENTATION OF THE WHOLE BODY

The studies hitherto discussed have focused on the upper limb, providing converging evidence for the multisensory integrative mechanisms that assist the construction and maintenance of a coherent central representation of the hand that, in turn, may support the feeling of ownership of the hand itself. Nevertheless, it goes without saying that these self-specifying multisensory mechanisms must extend to the self-attribution of the whole body. However, it wasn't until very recently that experimental paradigms were available that demonstrate the role of multisensory processes in the self-attribution of the whole body (Petkova and Ehrsson, 2008; Slater et al., 2009; Petkova et al., 2011b; van der Hoort et al., 2011).

In a recent sequence of experiments, Petkova and colleagues showcased a behavioral paradigm that extends the principles first outlined in the description of the rubber hand illusion (Botvinick and Cohen, 1998) to the self-perception of the whole body (Petkova and Ehrsson, 2008; Petkova et al., 2011b). In this paradigm, the dynamic integration of synchronous visual and tactile stimuli delivered to the body of a humanoid mannequin seen from the first person perspective and to the participant's real body, respectively, elicits the feeling of ownership of the mannequin's body (Petkova and Ehrsson, 2008). In summary, the principles that support the feeling of ownership of the whole body closely resemble those that underpin the self-attribution of the hand, discussed in-depth in the studies presented in the thesis. Does that same relationship hold true with respect to the underlying neural mechanisms?

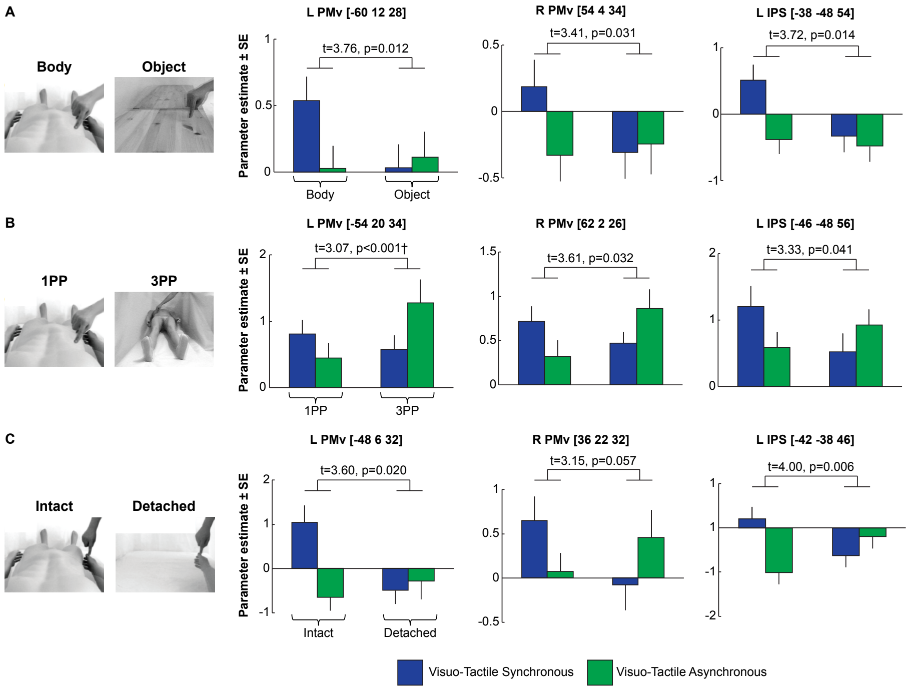

Figure 22. (**A**) The integration of visuo-tactile signals in multisensory areas of the premotor and parietal cortices is selective for spatio-temporally congruent signals originating from a humanoid body, as opposed to incongruent signals and/or signals originating from an object that does not resemble a human body (Petkova et al., 2011a). (**B**) The above multisensory integrative mechanisms operate in a body-part-centered reference frame that requires the first person visual perspective (1PP), as opposed to the third person perspective (3PP). † uncorrected for multiple comparisons. (**C**) The perception of an entire body, as opposed to the anatomically implausible condition depicting an artificial detached hand, is essential for the integration of congruent visuo-tactile signals that leads to the self-attribution of the whole body.

In a series of three fMRI experiments on healthy volunteers (Petkova et al., 2011a), we recently demonstrated that the self-attribution of the whole body is associated with the integration of visual, tactile, and proprioceptive signals in a set of frontal, parietal, and subcortical brain regions (Figure 22). The neuroanatomical and functional features of these findings bore a compelling similarity to those from the experiments presented in this thesis, hinting at a neural representation of the whole body other than the collection of the segmented representation of its parts, such as the limbs (Blanke and Metzinger, 2009; Tsakiris, 2010; Petkova et al., 2011a; Ehrsson, 2012). This observation solicits an obvious follow-up question: is there something to the neural mechanisms underpinning the self-attribution of the whole body that goes beyond the sum of its individual parts? In other words, how can the emergence of the perceptual whole body gestalt be related to the neural mechanisms described above?

An intriguing hypothesis concerning the basic mechanisms that might facilitate the formation of a multisensory whole-body gestalt traces back to the neurophysiological evidence summarized in the Introduction. Amongst the multisensory neurons identified in the posterior parietal and premotor cortices of the non-human primate brain, specific populations are equipped with visuo-tactile receptive fields that span multiple body segments or, in some cases, encompass the entire body and its surrounding peripersonal space (Rizzolatti et al., 1981a, 1981b; Fogassi et al., 1996; Duhamel et al., 1998; Graziano and Gandhi, 2000; Graziano et al., 2000). The partaking of these neuronal populations in the integration of multisensory bodily signals might constitute the neural mechanism that enables the construction of a unified representation of the body, which in turn results in the self-attribution of the whole body (Petkova et al., 2011a). Interestingly, recent behavioral and neuroimaging evidence supports the hypothesis presented above (Petkova and Ehrsson, 2008; Petkova et al., 2011a; Gentile et al., unpublished data in preparation).

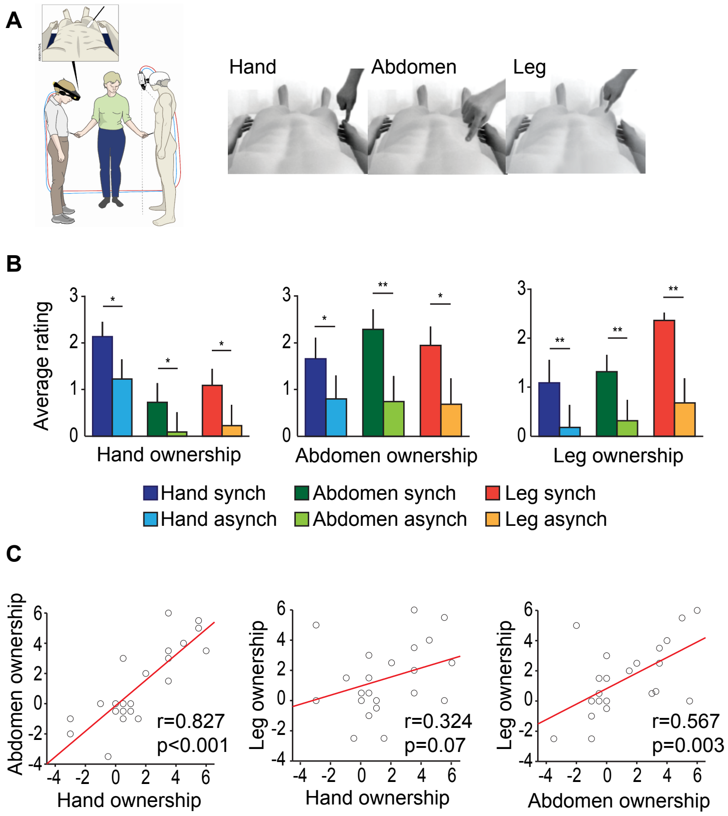

Figure 23. (**A**) Left: the setup employed to induce the self-attribution of a whole body in the study of Petkova and Ehrsson (Petkova and Ehrsson, 2008; adapted from Ehrsson, 2012). Right: we conducted a series of behavioral and neuroimaging experiments where the self-attribution of a whole body was induced via the delivery of congruent visuo-tactile stimuli to the hand, abdomen, or leg of a humanoid mannequin and to the corresponding part of the participant's body, respectively. (**B**) The feeling of ownership of the stimulated body part spreads to encompass the non-stimulated body parts, in line with the existence of a multisensory body gestalt. *p<0.05, **p<0.01. (**C**) The more vivid the self-attribution of the stimulated body part, the stronger the feeling of ownership that encompasses the other body parts.

First, the subjective experience of ownership of a single stimulated body-part spreads to encompass the whole body (Petkova et al., 2008; Gentile et al., in preparation; see Figure 23). Second, multivoxel pattern analyses of the neuroimaging data summarized above revealed that the patterns of BOLD activity within a region of the ventral premotor cortex contain information about the integration of visuo-tactile stimuli from a self-attributed body that generalizes across two different body segments, the hand and the abdomen (Petkova et al., 2011a). These results were further extended in a recent study that provided two additional conclusions (Gentile et al., in preparation). First, we identified neuronal populations in a region of the ventral premotor cortex with receptive fields large enough to encompass three different body parts, namely the abdomen, the hand, and the leg.

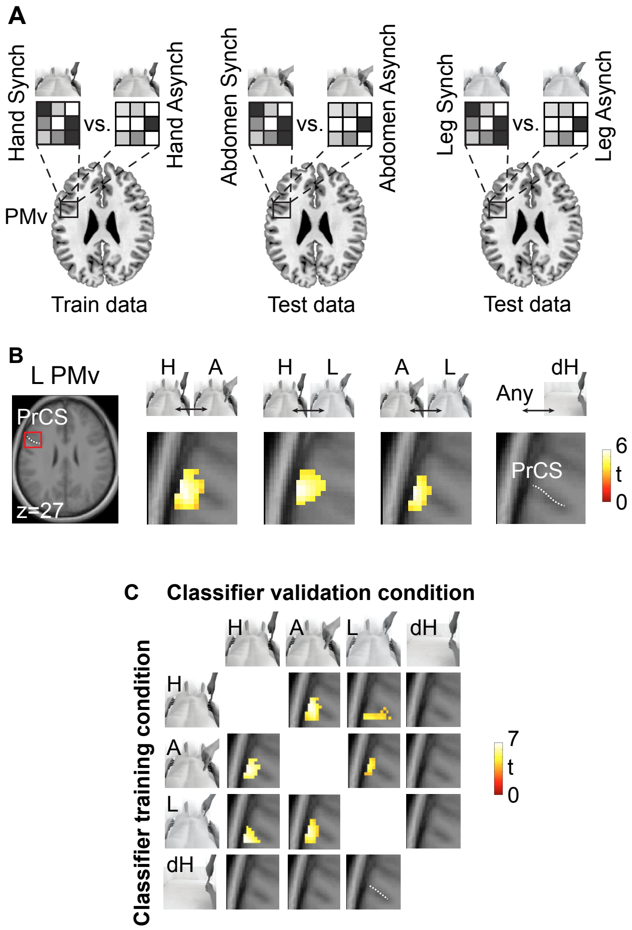

Figure 24. (**A**) We performed an fMRI experiment on sixteen healthy volunteers and we induced the illusory self-attribution of a mannequin's body by delivering synchronous, as opposed to asynchronous, visuo-tactile stimuli to the hand (H), abdomen (A), and leg (L). We employed multivoxel pattern analysis (Björnsdotter et al., 2011; Petkova et al., 2011a) to identify patterns of BOLD activity that distinguish between self-attributed multisensory stimuli, as opposed to the asynchronous control condition, and that generalize significantly across all three body segments (Gentile et al., in preparation). (**B**, **C**) A region in the ventral premotor cortex, centered on the inferior segment of the precentral sulcus (PrCS), generalized significantly across all body parts, but only in the context of an intact body, as opposed to the condition featuring an anatomically implausible detached hand (dH).

Crucially, the multivoxel patterns of the BOLD signal measured in this region were specific for the congruent visuo-tactile signals deriving from a self-attributed body part and generalized significantly across all body segments (Figure 24), consistently with their role in the construction of a whole body perceptual gestalt. Importantly, this generalization was significantly abolished if the multisensory stimuli were incongruent and/or if they appeared to originate from the virtual image of an artificial detached hand (Figure 24). Conversely, we found preliminary evidence for the existence of neuronal populations in different segments of the premotor and the posterior parietal cortices, as well as the putamen, that integrate multisensory signals in a body-part-specific fashion (Gentile et al., in preparation), in keeping with the existence of multisensory neurons with visuo-tactile receptive fields restricted to a specific body segments (Rizzolatti et al., 1981a, 1981b; Graziano and Gandhi, 2000; Graziano and Botvinick, 2002).

These initial findings suggest that neuronal populations in frontal, parietal, and subcortical areas integrate multisensory signals from the body in a body-part-specific fashion, supported by the properties of their visuo-tactile receptive fields. Conversely, putative multisensory neuronal populations in the ventral premotor cortex equipped with visuo-tactile receptive fields encompassing multiple segments of the body may be decisive in the formation of the whole-body perceptual gestalt that underlies the behavioral effects summarized above. Future research should expand on these initial findings to characterize the visuo-tactile receptive fields of multisensory neurons, as well as their causal role in the emergence of a multisensory representation of the whole body and the associated perceptual gestalt.

6.6 HOW MALLEABLE IS THE REPRESENTATION OF THE BODY?

The existence of perceptual illusions like the rubber hand illusion (Botvinick and Cohen, 1998), the “third arm” illusion (Guterstam et al., 2011), the whole-body illusion (Petkova and Ehrsson, 2008), the “enfacement effect” (Paladino et al., 2010; Sforza et al., 2010), and the “out-of-body” illusion (Ehrsson, 2007; Lenggenhager et al., 2007) reveals that the central representation of the body is considerably more plastic than what was previously thought. The interplay of multisensory integration and higher-order representations preserves and, if necessary, updates the representation of the body to attain coherence by incorporating artificial limbs or whole bodies and by remapping the perceived spatial boundaries of the self. However, higher-order representations set limits to the malleability of the bodily self that reflect innate and acquired knowledge of the morphology and appearance of the human body (Tsakiris et al., 2010a; Apps and Tsakiris, 2013). But just how far do the plastic boundaries of the bodily self extend?

In a recent set of experiments, we described an uncanny perceptual illusion whereby healthy participants refer somatic sensations to and embody a discrete volume of empty space (Guterstam et al., 2013). In this "invisible hand" illusion, the integration of visual and tactile signals that are congruent in time and in hand-centered coordinates is so powerful that it overrides the ostensibly obvious fact that no hand is present in the space in direct view of the participant (Figure 25). The experience of the illusion is associated with increased activity in the multisensory regions of the premotor, posterior parietal, and cerebellar cortices characterized in the studies presented here (Figure 25).

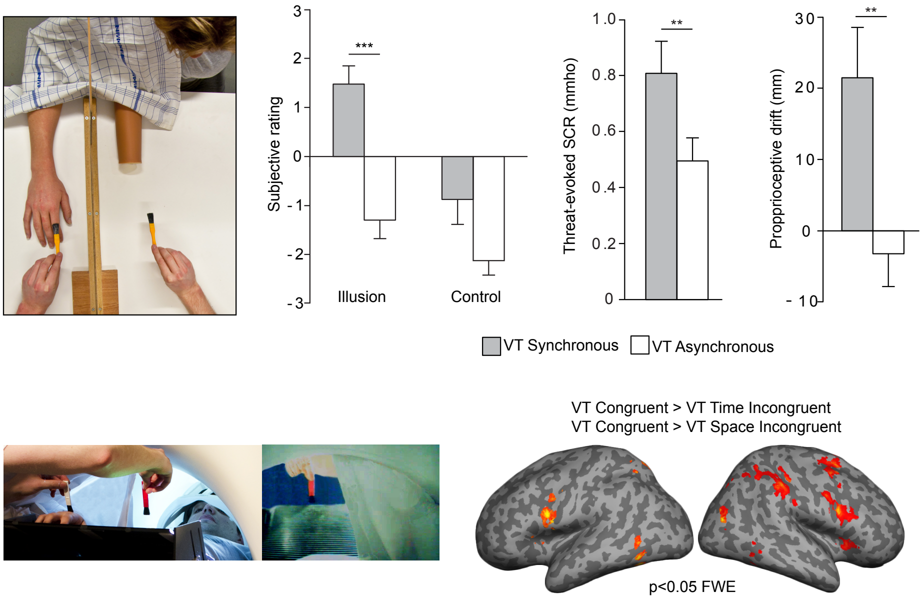

Figure 25. The integration of temporally synchronous and anatomically congruent tactile signals from the occluded right hand and visual signals from the empty space in direct view of the participants leads to the uncanny referral of somatic sensations to the empty space, which is felt as part of one's physical body (the "invisible hand" illusion). This phenomenon was characterized using converging behavioral, psychophysiological, and BOLD measures. Adapted from (Guterstam et al., 2013).

These findings offer an important conclusion: when the multisensory criteria of spatial and temporal congruence within the perihand space are met, the bottom-up integration of the sensory signals plays a formidable role in redefining the spatial boundaries of the body. Nevertheless, at a first glance these findings appear to be at odds with the notion that prior knowledge about the structure and appearance of the body poses a limit to the plasticity of the neural representation of the body itself (Petkova and Ehrsson, 2008; Tsakiris, 2010; Tsakiris et al., 2010a; Petkova et al., 2011a). How can the description of this perceptual illusion be reconciled with the role of higher-order multisensory predictions that should, intuitively, prevent the remapping of the spatial boundaries of the body to incorporate a portion of empty space?

An insight concerning the answer to this question comes from the observation that the peripersonal space embraces the array of anatomically plausible locations of the limbs, with the exception of the spatial locations that are occupied by non-corporeal objects (Guterstam et al., 2011, 2013). Furthermore, the spatial localization of the hand relies on mechanisms that are not exclusively tied to the dominance of visual inputs. The spatio-temporal correlation between many different pairs of sensory modalities, like visuo-proprioceptive (Lackner and Shenker, 1985; Lackner and DiZio, 2000; Walsh et al., 2011), tactile-proprioceptive (Ehrsson et al., 2005; Petkova et al., 2012), and visuo-motor (Tsakiris, 2010; Tsakiris et al., 2010b; Kalckert and Ehrsson, 2012), have all been shown to play a key role in localizing and self-attributing the hand in space. Hence, it is conceivable that the patterns of multisensory correlations associated with the invisible hand illusion might engage one of the mechanisms that operate to help localize the limbs in space; save the case of clear anatomical implausibility, the perceived location of the limb can then be remapped to a portion of the empty peripersonal space, alongside the updating of the higher-order predictions that dynamically assign weights to the different sensory inputs (Ernst and Banks, 2002; Fetsch et al., 2012; Apps and Tsakiris, 2013; Guterstam et al., 2013). The above speculations signal the need for further research aimed at shedding light on the interplay between bottom-up sensory inputs and top-down multisensory expectations. As suggested in the interpretation of the findings from Study V and the associated theoretical accounts (Friston, 2009; den Ouden et al., 2012; Apps and Tsakiris, 2013; Clark, 2013; Limanowski and Blankenburg, 2013), this functional interplay plays a key role in maintaining and updating the multisensory neural representation of the body. However, much remains to be investigated about these mechanisms, as exemplified by the open questions raised by phenomena like the “invisible hand illusion”.

6.7 CONCLUDING REMARKS

In conclusion, the work presented in this thesis has attempted to gather evidence in support of the notion that the human brain constructs a coherent central representation of the hand in space by integrating congruent visual, tactile, and proprioceptive signals. Moreover, the studies were designed to offer evidence of the relationship between the multisensory representation of the hand and the feeling of ownership of the limb. The methodologies, particularly with respect to the use of functional magnetic resonance imaging, psychometric, and psychophysiological measurements, were summarized and discussed critically, outlining the strengths and weaknesses of the studies. The results from functional magnetic resonance imaging experiments in healthy humans suggested that the human brain constructs a representation of the hand by integrating congruent visual, somatosensory, and proprioceptive signals in regions of the posterior parietal and premotor cortices, and, subcortically, in the cerebellar hemispheres and in the putamina. Furthermore, the data advocated the notion that the above brain regions contain neuronal populations with visual RFs restricted to the immediate space around the hand and spatially anchored to it, providing a mechanism for the representation of the perihand space. Converging behavioral, physiological, and neural data proposed a role for the multisensory representation of the hand in space in supporting the feeling of ownership of the hand. The results were discussed in conjunction with other pertinent findings to position them within the broader context of existing relevant knowledge in neurophysiology, neurology, experimental psychology, and cognitive neuroscience, and to help identify outstanding open questions for future research.

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